



Clinical trial results:

A multicenter, randomized, 52-week, double-blind, parallel-group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma

Summary

| | |
|--------------------------|---|
| EudraCT number | 2015-002899-25 |
| Trial protocol | EE LT DE SK PT AT HU NL FI BE ES DK LV GR FR BG IE HR SI IT |
| Global end of trial date | 14 June 2019 |

Results information

| | |
|--------------------------------|---|
| Result version number | v3 (current) |
| This version publication date | 21 May 2021 |
| First version publication date | 28 June 2020 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Additional text added in the field Adverse Events reporting additional description. |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CQVM149B2302 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02571777 |
| 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, Novartis.email@novartis.com |
| 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 | 14 June 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d., all delivered via Concept1 in terms of trough Forced Expiratory Volume in 1 second (FEV1) after 26 weeks of treatment in patients with asthma.

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.

At Visit 1, all patients were provided with a SABA (100 µg salbutamol/90 µg albuterol) via metered-dose inhaler (MDI) which they were instructed to use throughout the study as rescue medication.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 08 December 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 | Slovakia: 76 |
| Country: Number of subjects enrolled | South Africa: 46 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Sweden: 12 |
| Country: Number of subjects enrolled | Switzerland: 14 |
| Country: Number of subjects enrolled | Thailand: 31 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Vietnam: 28 |
| Country: Number of subjects enrolled | Jordan: 7 |
| Country: Number of subjects enrolled | Argentina: 424 |
| Country: Number of subjects enrolled | Austria: 19 |
| Country: Number of subjects enrolled | Belgium: 42 |
| Country: Number of subjects enrolled | Bulgaria: 59 |
| Country: Number of subjects enrolled | Canada: 37 |
| Country: Number of subjects enrolled | Chile: 58 |
| Country: Number of subjects enrolled | China: 66 |
| Country: Number of subjects enrolled | Colombia: 16 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Croatia: 11 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Estonia: 29 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 208 |
| Country: Number of subjects enrolled | Greece: 57 |
| Country: Number of subjects enrolled | Hungary: 142 |
| Country: Number of subjects enrolled | India: 392 |
| Country: Number of subjects enrolled | Ireland: 7 |
| Country: Number of subjects enrolled | Israel: 97 |
| Country: Number of subjects enrolled | Italy: 31 |
| Country: Number of subjects enrolled | Japan: 78 |
| Country: Number of subjects enrolled | Latvia: 60 |
| Country: Number of subjects enrolled | Lebanon: 7 |
| Country: Number of subjects enrolled | Lithuania: 75 |
| Country: Number of subjects enrolled | Mexico: 47 |
| Country: Number of subjects enrolled | Netherlands: 33 |
| Country: Number of subjects enrolled | Peru: 26 |
| Country: Number of subjects enrolled | Philippines: 55 |
| Country: Number of subjects enrolled | Poland: 161 |
| Country: Number of subjects enrolled | Portugal: 10 |
| Country: Number of subjects enrolled | Romania: 132 |
| Country: Number of subjects enrolled | Russian Federation: 435 |
| Worldwide total number of subjects | 3092 |
| EEA total number of subjects | 1228 |

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) | 2523 |
| From 65 to 84 years | 569 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in 415 investigative sites in 41 countries.

Pre-assignment

Screening details:

4851 participants were screened of which 3092 participants were randomized to 1 of the 5 treatment groups with a randomization ratio of 1:1:1:1:1.

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 | Investigator, Data analyst, Assessor, Subject |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | QVM149 150/50/160 µg o.d. |

Arm description:

QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium bromide/mometasone furoate) |
| Investigational medicinal product code | QVM149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Once daily (o.d.) delivered via Concept1 device

| | |
|------------------|--------------------------|
| Arm title | QVM149 150/50/80 µg o.d. |
|------------------|--------------------------|

Arm description:

QVM149 150/50/80 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | QVM149 150/50/80 µg (indacaterol acetate/glycopyrronium bromide/mometasone furoate) |
| Investigational medicinal product code | QVM149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Once daily (o.d.) delivered via Concept1 device

| | |
|------------------|------------------------|
| Arm title | QMF149 150/320 µg o.d. |
|------------------|------------------------|

Arm description:

QMF149 150/320 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|---|--|
| Investigational medicinal product name | QMF149 150/320 µg (indacaterol acetate/mometasone furoate) |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Once daily (o.d.) delivered via Concept1 device | |
| Arm title | QMF149 150/160 µg o.d. |

Arm description:

QMF149 150/160 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|---|--|
| Arm type | Active comparator |
| Investigational medicinal product name | QMF149 150/160 µg (indacaterol acetate/mometasone furoate) |
| Investigational medicinal product code | QMF149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Once daily (o.d.) delivered via Concept1 device | |
| Arm title | Salmeterol/fluticasone 50/500 µg b.i.d. |

Arm description:

Salmeterol xinafoate /fluticasone propionate 50/500 µg twice daily (b.i.d.) delivered via Accuhaler®

| | |
|---|--|
| Arm type | Active comparator |
| Investigational medicinal product name | QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium/mometasone furoate) |
| Investigational medicinal product code | QVM149 |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Twice daily (b.i.d.) delivered via Accuhaler® | |

| Number of subjects in period 1 | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. |
|---------------------------------------|------------------------------|-----------------------------|---------------------------|
| Started | 619 | 620 | 618 |
| Full Analysis Set (FAS) | 615 | 616 | 611 |
| Safety Set (SAF) | 616 | 617 | 613 |
| Completed | 580 | 582 | 577 |
| Not completed | 39 | 38 | 41 |
| Adverse event, serious fatal | 1 | 1 | 4 |
| Physician decision | 1 | 7 | 5 |
| Protocol Deviation | 2 | 3 | 4 |
| Pregnancy | - | - | - |
| Lost to follow-up | 1 | 1 | 2 |
| Subject/guardian decision | 34 | 26 | 26 |

| Number of subjects in period 1 | QMF149 150/160 µg o.d. | Salmeterol/fluticasone 50/500 µg b.i.d. |
|---------------------------------------|-----------------------------------|--|
| Started | 617 | 618 |
| Full Analysis Set (FAS) | 607 | 612 |
| Safety Set (SAF) | 608 | 618 |
| Completed | 580 | 582 |
| Not completed | 37 | 36 |
| Adverse event, serious fatal | - | - |
| Physician decision | 2 | 4 |
| Protocol Deviation | 8 | 4 |
| Pregnancy | 2 | - |
| Lost to follow-up | - | 1 |
| Subject/guardian decision | 25 | 27 |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | QVM149 150/50/160 µg o.d. |
| Reporting group description: QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QVM149 150/50/80 µg o.d. |
| Reporting group description: QVM149 150/50/80 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QMF149 150/320 µg o.d. |
| Reporting group description: QMF149 150/320 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QMF149 150/160 µg o.d. |
| Reporting group description: QMF149 150/160 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | Salmeterol/fluticasone 50/500 µg b.i.d. |
| Reporting group description: Salmeterol xinafoate /fluticasone propionate 50/500 µg twice daily (b.i.d.) delivered via Accuhaler® | |

| Reporting group values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. |
|---|------------------------------|-----------------------------|---------------------------|
| Number of subjects | 619 | 620 | 618 |
| 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) | 507 | 504 | 514 |
| From 65-84 years | 112 | 116 | 104 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 52.1 | 52.4 | 52.0 |
| standard deviation | ± 12.91 | ± 12.71 | ± 12.81 |
| Sex: Female, Male Units: Participants | | | |
| Female | 381 | 362 | 380 |
| Male | 238 | 258 | 238 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 456 | 458 | 453 |
| Black | 4 | 5 | 3 |

| | | | |
|-----------------|-----|-----|-----|
| Asian | 139 | 133 | 133 |
| Native American | 7 | 8 | 8 |
| Unknown | 0 | 0 | 0 |
| Other | 13 | 16 | 21 |

| Reporting group values | QMF149 150/160 µg o.d. | Salmeterol/fluticasone 50/500 µg b.i.d. | Total |
|---|---------------------------|---|-------|
| Number of subjects | 617 | 618 | 3092 |
| 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) | 502 | 496 | 2523 |
| From 65-84 years | 115 | 122 | 569 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 51.8 | 52.9 | |
| standard deviation | ± 12.86 | ± 12.23 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 378 | 417 | 1918 |
| Male | 239 | 201 | 1174 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 452 | 468 | 2287 |
| Black | 4 | 1 | 17 |
| Asian | 135 | 131 | 671 |
| Native American | 4 | 5 | 32 |
| Unknown | 1 | 0 | 1 |
| Other | 21 | 13 | 84 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | QVM149 150/50/160 µg o.d. |
| Reporting group description: QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QVM149 150/50/80 µg o.d. |
| Reporting group description: QVM149 150/50/80 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QMF149 150/320 µg o.d. |
| Reporting group description: QMF149 150/320 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | QMF149 150/160 µg o.d. |
| Reporting group description: QMF149 150/160 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device | |
| Reporting group title | Salmeterol/fluticasone 50/500 µg b.i.d. |
| Reporting group description: Salmeterol xinafoate /fluticasone propionate 50/500 µg twice daily (b.i.d.) delivered via Accuhaler® | |

Primary: Trough Forced Expiratory Volume in 1 Second (Trough FEV1) of QVM149 versus QMF149 at week 26

| | |
|---|--|
| End point title | Trough Forced Expiratory Volume in 1 Second (Trough FEV1) of QVM149 versus QMF149 at week 26 |
| End point description: Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. The primary endpoint considered the following 2 comparison groups: - QVM149 150/50/80 µg o.d. compared with QMF149 150/160 µg o.d. both delivered via Concept1 - QVM149 150/50/160 µg o.d. compared with QMF149 150/320 µg o.d. both delivered via Concept1. | |
| End point type | Primary |
| End point timeframe: 26 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 614 | 614 | 606 | 602 |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 2.050 (± 0.0128) | 2.029 (± 0.0129) | 1.984 (± 0.0129) | 1.953 (± 0.0130) |

| | | | | |
|-------------------------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 607 | | | |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 1.930 (± 0.0131) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QMF149 150/320 µg o.d. v QVM149 150/50/160 µg o.d. |
| Number of subjects included in analysis | 1220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed Model for Repeated Measures (MMRM) |
| Parameter estimate | LS Mean |
| Point estimate | 0.065 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.031 |
| upper limit | 0.099 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0176 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1216 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.076 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.041 |
| upper limit | 0.111 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0176 |

Secondary: Asthma Control Questionnaire (ACQ-7) at Week 26 and Week 52

| | |
|-----------------|---|
| End point title | Asthma Control Questionnaire (ACQ-7) at Week 26 and Week 52 |
|-----------------|---|

End point description:

The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV1, 1 = 90 - 95%, 2 = 80 - 89%, 3 = 70 - 79%, 4 = 60 - 69%, 5 = 50 - 59%, and Score = 6 means < 50% of predicted FEV1). The ACQ-7 total score reported below was calculated as the mean of scores of all 7 items and ranged between 0 and 6, with higher scores indicating worse asthma symptom control.

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

End point timeframe:

26 weeks, 52 weeks

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 607 | 595 | 596 | 598 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 1.542 (± 0.0329) | 1.543 (± 0.0330) | 1.528 (± 0.0329) | 1.614 (± 0.0331) |
| Week 52 | 1.406 (± 0.0334) | 1.535 (± 0.0337) | 1.465 (± 0.0335) | 1.545 (± 0.0338) |

| End point values | Salmeterol/fluti casone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 599 | | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 1.628 (± 0.0329) | | | |
| Week 52 | 1.527 (± 0.0335) | | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|----------------------------|---|

| | |
|---|--|
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.729 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.066 |
| upper limit | 0.094 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0406 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.034 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.086 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.165 |
| upper limit | -0.006 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0404 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.085 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.071 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.151 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0409 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1194 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.084 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.164 |
| upper limit | -0.005 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0406 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.157 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.059 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.14 |
| upper limit | 0.023 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0415 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.121 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.202 |
| upper limit | -0.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0414 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1193 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.814 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.092 |
| upper limit | 0.072 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.042 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1194 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.845 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.008 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.073 |
| upper limit | 0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0416 |

Secondary: Trough Forced Expiratory Volume in 1 Second (Trough FEV1) of QVM149 versus salmeterol/fluticasone at week 26

| | |
|-----------------|--|
| End point title | Trough Forced Expiratory Volume in 1 Second (Trough FEV1) of QVM149 versus salmeterol/fluticasone at week 26 |
|-----------------|--|

End point description:

Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing.

This secondary endpoint considered the following 2 comparison groups:

- QVM149 150/50/80 µg o.d. via Concept1 compared with salmeterol/fluticasone 50/500 µg b.i.d. via Accuhaler®
- QVM149 150/50/160 µg o.d. via Concept 1 compared with salmeterol/fluticasone 50/500 µg b.i.d. via Accuhaler®

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

End point timeframe:

26 weeks

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 614 | 614 | 606 | 602 |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 2.050 (± 0.0128) | 2.029 (± 0.0129) | 1.984 (± 0.0129) | 1.953 (± 0.0130) |

| | | | | |
|-------------------------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 607 | | | |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 1.930 (± 0.0131) | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.119 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.085 |
| upper limit | 0.154 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0177 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.099 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.064 |
| upper limit | 0.133 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0177 |

Secondary: Trough FEV1 at week 52

| | |
|---|------------------------|
| End point title | Trough FEV1 at week 52 |
| End point description: Trough FEV1 was assessed by performing spirometric assessment. It is defined as average of the two FEV1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. | |
| End point type | Secondary |
| End point timeframe: 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 614 | 614 | 606 | 602 |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 2.050 (± 0.0129) | 1.992 (± 0.0130) | 1.965 (± 0.0130) | 1.930 (± 0.0130) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 607 | | | |
| Units: litre (L) | | | | |
| least squares mean (standard error) | 1.905 (± 0.0132) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.086 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.051 |
| upper limit | 0.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0176 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.145 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.111 |
| upper limit | 0.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0178 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1216 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.062 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.027 |
| upper limit | 0.096 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0178 |

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
|-----------------------------------|--------------------------------------|

| | |
|---|--|
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.087 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.052 |
| upper limit | 0.122 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0179 |

Secondary: Pre-dose Forced Vital Capacity (FVC) at week 4 and week 12

| | |
|--|--|
| End point title | Pre-dose Forced Vital Capacity (FVC) at week 4 and week 12 |
| End point description: | |
| Pre-dose FVC is defined as average of the two FVC measurements taken 45 min and 15 min pre evening dose. It was assessed by performing spirometric assessment. FVC is the total amount of air exhaled during the FEV test. | |
| End point type | Secondary |
| End point timeframe: | |
| 4 weeks, 12 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 606 | 594 | 592 | 596 |
| Units: litre (L) | | | | |
| least squares mean (standard error) | | | | |
| Week 4 | 3.091 (± 0.0161) | 3.059 (± 0.0163) | 3.018 (± 0.0163) | 3.020 (± 0.0163) |
| Week 12 | 3.067 (± 0.0162) | 3.065 (± 0.0164) | 3.011 (± 0.0163) | 3.014 (± 0.0164) |

| End point values | Salmeterol/fluti casone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 598 | | | |
| Units: litre (L) | | | | |
| least squares mean (standard error) | | | | |

| | | | | |
|---------|-----------------------|--|--|--|
| Week 4 | 2.952 (\pm 0.0163) | | | |
| Week 12 | 2.965 (\pm 0.0163) | | | |

Statistical analyses

| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|---|--|
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.073 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 0.116 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0218 |

| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
|---|---|
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.139 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.096 |
| upper limit | 0.181 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0217 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.074 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.004 |
| upper limit | 0.082 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.022 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.108 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.065 |
| upper limit | 0.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0219 |

| | |
|-----------------------------------|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.014 |
| upper limit | 0.099 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0219 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.102 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.059 |
| upper limit | 0.145 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0218 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.022 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.05 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.007 |
| upper limit | 0.094 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0221 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 12 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.099 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.056 |
| upper limit | 0.142 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.022 |

Secondary: Trough Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) at 52 weeks

| | |
|--|---|
| End point title | Trough Forced Expiratory Flow (FEF) between 25% and 75% of FVC (FEF25-75) at 52 weeks |
| End point description: FEF is the flow (or speed) of air coming out of the lung during the middle portion of a forced expiration. Trough FEF25-75% is defined as average of the two FEF25-75% measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. It was assessed by performing spirometric assessment. | |
| End point type | Secondary |
| End point timeframe: Up to Week 52 | |

| | | | | |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 614 | 614 | 606 | 602 |
| Units: L/s | | | | |
| least squares mean (standard error) | 1.354 (± 0.0190) | 1.263 (± 0.0192) | 1.260 (± 0.0191) | 1.214 (± 0.0192) |

| | | | | |
|-------------------------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 607 | | | |
| Units: L/s | | | | |
| least squares mean (standard error) | 1.207 (± 0.0194) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.095 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.045 |
| upper limit | 0.145 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0254 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.147 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.097 |
| upper limit | 0.198 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0256 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1216 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.057 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.049 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.001 |
| upper limit | 0.099 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0256 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.029 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.006 |
| upper limit | 0.107 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0258 |

Secondary: Change from baseline in morning and evening Peak Expiratory Flow Rate (PEF) over 26 and 52 weeks of treatment

| | |
|-----------------|---|
| End point title | Change from baseline in morning and evening Peak Expiratory Flow Rate (PEF) over 26 and 52 weeks of treatment |
|-----------------|---|

End point description:

PEF is a person's maximum speed of expiration. All the participants were instructed to record PEF twice daily using a mini Peak Flow Meter device, once in the morning (before taking the morning dose) and once approximately 12 h later in the evening (before taking the evening dose) at home. At each timepoint, the participant was instructed to perform 3 consecutive manoeuvres within 10 minutes. These PEF values were captured in the e-PEF/diary. The best of 3 values were used.

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

End point timeframe:

Baseline, 26 weeks, 52 weeks

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 596 | 584 | 581 | 584 |
| Units: L/min | | | | |
| least squares mean (standard error) | | | | |
| Week 26 - Mean morning PEF | 47.7 (± 1.93) | 40.5 (± 1.95) | 29.5 (± 1.95) | 25.6 (± 1.95) |
| Week 26 - Mean evening PEF | 39.6 (± 1.87) | 34.7 (± 1.88) | 22.8 (± 1.88) | 20.6 (± 1.89) |
| Week 52 - Mean morning PEF | 47.5 (± 2.03) | 41.2 (± 2.05) | 28.8 (± 2.05) | 25.6 (± 2.06) |
| Week 52 - Mean evening PEF | 38.7 (± 1.97) | 35.0 (± 1.99) | 21.2 (± 1.99) | 20.1 (± 2.00) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 586 | | | |
| Units: L/min | | | | |
| least squares mean (standard error) | | | | |
| Week 26 - Mean morning PEF | 12.5 (± 1.95) | | | |
| Week 26 - Mean evening PEF | 10.4 (± 1.89) | | | |
| Week 52 - Mean morning PEF | 12.7 (± 2.05) | | | |
| Week 52 - Mean evening PEF | 9.2 (± 1.99) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Week 26 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Linear Mixed Model (LMM) |
| Parameter estimate | LS Mean |
| Point estimate | 18.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.2 |
| upper limit | 23.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.59 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 35.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 30.2 |
| upper limit | 40.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.58 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 26 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 14.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.8 |
| upper limit | 20 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.61 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.9 |
| upper limit | 33.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.6 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Week 26 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 16.8 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.8 |
| upper limit | 21.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.53 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 29.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 24.2 |
| upper limit | 34.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.53 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 26 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 14.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.1 |
| upper limit | 19.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.55 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 24.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.3 |
| upper limit | 29.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.54 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Week 52 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 18.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.4 |
| upper limit | 24.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.72 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 |

| | |
|---|----------------------------|
| | µg b.i.d. |
| Number of subjects included in analysis | 1182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 34.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 29.5 |
| upper limit | 40.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.7 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 52 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 15.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.2 |
| upper limit | 20.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.74 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 - Mean morning PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 28.5 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 23.2 |
| upper limit | 33.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.72 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Week 52 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1177 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 17.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.3 |
| upper limit | 22.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.66 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 29.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 24.2 |
| upper limit | 34.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.66 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 52 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.7 |
| upper limit | 20.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.69 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 - Mean evening PEF | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 25.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.5 |
| upper limit | 31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.68 |

Secondary: Change from baseline in percentage of asthma symptom-free days over 52 weeks

| | |
|-----------------|--|
| End point title | Change from baseline in percentage of asthma symptom-free days over 52 weeks |
|-----------------|--|

End point description:

All participants were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. Asthma symptoms free days are days with no daytime symptoms, no night-time awakenings and no symptoms on awakening. The daytime asthma symptom score was based on the daily e-diary recordings by participants with respect to shortness of breath, wheeze, cough, chest tightness, and impact on usual daily activities due to symptoms.

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

End point timeframe:

Baseline, 52 weeks

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 566 | 552 | 559 | 554 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 22.4 (± 1.35) | 18.0 (± 1.36) | 22.2 (± 1.36) | 18.0 (± 1.37) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 558 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 18.9 (± 1.36) | | | |

Statistical analyses

| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|---|--|
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.907 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 3.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.81 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.055 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.81 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.997 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 3.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.83 |

| | |
|-----------------------------------|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1110 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.606 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.82 |

Secondary: Change from baseline in percentage of days with no daytime symptoms

| | |
|---|---|
| End point title | Change from baseline in percentage of days with no daytime symptoms |
| End point description: | |
| All participants were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. For days with no daytime symptoms, all 5 evening questions must have a score = 0 with respect to shortness of breath, wheeze, cough, chest tightness and impact on usual daily activities due to symptoms, each with scores from 0 (no problems) to 4 (very severe problems). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 594 | 577 | 579 | 579 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 22.5 (± 1.32) | 17.9 (± 1.34) | 21.8 (± 1.33) | 18.0 (± 1.34) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 578 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 18.8 (± 1.34) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.712 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | 4.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 7.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.943 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.7 |
| upper limit | 3.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.8 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.612 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.4 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.79 |

Secondary: Change from baseline in percentage of nights with no night-time awakenings over 52 weeks

| | |
|---|--|
| End point title | Change from baseline in percentage of nights with no night-time awakenings over 52 weeks |
| End point description: | |
| All participants were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. The question asked for nights with no night-time awakenings was "How did you sleep last night?" had to be answered with "I did not wake up because of any breathing problems" with scores from 0 (no problem)-4 (very severe problems). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 599 | 584 | 582 | 584 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 18.0 (± 1.11) | 17.6 (± 1.12) | 18.4 (± 1.13) | 16.1 (± 1.13) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 586 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 16.9 (± 1.12) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.809 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.51 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.467 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.5 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.318 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 4.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.52 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.64 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 3.7 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.51 |

Secondary: Change from baseline in percentage of mornings with no symptoms on rising over 52 weeks

| | |
|-----------------|---|
| End point title | Change from baseline in percentage of mornings with no symptoms on rising over 52 weeks |
|-----------------|---|

End point description:

All participants were provided with an electronic diary (e-Diary) to record clinical symptoms. They were instructed to routinely complete the e-Diary twice daily at the same time each morning and again approximately 12 hours later in the evening. The e-Diary was reviewed at each visit until study completion. The question asked for nights with no night-time awakenings was "How did you sleep last night?" had to be answered with "I did not wake up because of any breathing problems" with scores from 0 (no problem)-4 (very severe problems).

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

End point timeframe:

Baseline, 52 weeks

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 599 | 584 | 582 | 584 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 19.5 (± 1.33) | 18.5 (± 1.35) | 19.9 (± 1.35) | 15.5 (± 1.35) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 586 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 15.6 (± 1.34) | | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.814 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 3.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.83 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1185 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.036 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 7.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.83 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.098 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 6.7 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.84 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1170 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.118 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 6.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.84 |

Secondary: Change from baseline in percentage of days without rescue medication use over 26 and 52 weeks

| | |
|------------------------------|---|
| End point title | Change from baseline in percentage of days without rescue medication use over 26 and 52 weeks |
| End point description: | Percentage of days without rescue medication usage (100 µg salbutamol/90 µg albuterol via metered-dose inhaler) as recorded by e-diary over 26 and 52 weeks of treatment. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 26 weeks, 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 590 | 577 | 578 | 580 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 22.5 (± 1.32) | 19.5 (± 1.33) | 23.3 (± 1.33) | 18.2 (± 1.33) |
| Week 52 | 25.0 (± 1.36) | 21.9 (± 1.36) | 24.9 (± 1.36) | 20.8 (± 1.37) |

| | | | | |
|-------------------------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 579 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 19.6 (± 1.33) | | | |
| Week 52 | 21.8 (± 1.36) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.645 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.74 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 6.3 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.73 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.75 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.971 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 3.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.75 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|-----------------------------------|---|

| | |
|---|--|
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.963 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.075 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 6.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.77 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.517 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.79 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.956 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

Secondary: Percentage of patients achieving the minimal clinically important difference (MCID) ACQ ≥ 0.5 at Week 26 and Week 52

| | |
|-----------------|--|
| End point title | Percentage of patients achieving the minimal clinically important difference (MCID) ACQ ≥ 0.5 at Week 26 and Week 52 |
|-----------------|--|

End point description:

Change from baseline in ACQ-7 scores of ≤ 0.5 was defined as minimal clinically important difference and were considered clinically meaningful. The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV1 % predicted). All 7 questions of the ACQ-7 were equally weighted. Items 1-5 were scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item was scored by the investigator based on the FEV1 % predicted from the masterscope at the site (i.e., Score = 0 means $> 95\%$ of predicted FEV1, 1 = 90 - 95%, 2 = 80 - 89%, 3 = 70 - 79%, 4 = 60 - 69%, 5 = 50 - 59%, and Score = 6 means $< 50\%$ of predicted FEV1). The total score was calculated as the mean of all

questions.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 26 weeks, 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-----------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 26 | 71.2 | 71.7 | 74.2 | 70.7 |
| Week 52 | 78.8 | 72.8 | 77.9 | 73.1 |

| End point values | Salmeterol/fluti- casone 50/500 µg b.i.d. | | | |
|-----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 26 | 67.4 | | | |
| Week 52 | 72.8 | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.535 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.2 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.151 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.57 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.38 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.48 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.172 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.57 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.47 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.017 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.86 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.744 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.38 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.922 |
| Method | Logistic regression model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.29 |

Secondary: Time to first hospitalization for asthma exacerbation

| | |
|--|---|
| End point title | Time to first hospitalization for asthma exacerbation |
| End point description: | |
| Time from start of treatment until the first event (hospitalization for asthma exacerbation) or censoring. Patients without the event were considered as censored at the date of last treatment + 1 day. For patients having the event, the start date of the hospitalization was considered to calculate the time to event (i.e., the number of days from start of treatment up to the event start date). | |
| End point type | Secondary |

End point timeframe:

52 weeks on average, up to 416 days

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: days | | | | |
| median (full range (min-max)) | 367.0 (2 to 416) | 367.0 (2 to 396) | 367.0 (1 to 411) | 367.0 (1 to 408) |

| End point values | Salmeterol/fluti- casone 50/500 µg b.i.d. | | | |
|-------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: days | | | | |
| median (full range (min-max)) | 367.0 (1 to 416) | | | |

Statistical analyses

| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|---|--|
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.371 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 1.63 |

| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
|----------------------------|---|
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|-------------------|
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.996 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 2.66 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.145 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 4.47 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.15 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 4.43 |

Secondary: Time to first asthma exacerbation by exacerbation category

| | |
|-----------------|--|
| End point title | Time to first asthma exacerbation by exacerbation category |
|-----------------|--|

End point description:

Time from start of treatment until the first event (asthma exacerbation) or censoring. Patients without the event were considered as censored at the date of last treatment + 1 day. For patients having the event, the start date of the exacerbation was considered to calculate the time to event (i.e., the number of days from start of treatment up to the event start date).

The exacerbation categories were: All (mild, moderate and severe), combination of moderate or severe and severe.

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

End point timeframe:

52 weeks on average, up to 416 days

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|--|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Moderate or severe asthma exacerbation | 366.0 (2 to 416) | 366.0 (2 to 396) | 366.0 (1 to 411) | 365.0 (1 to 387) |
| Severe asthma exacerbation | 366.0 (2 to 416) | 366.0 (2 to 396) | 366.0 (1 to 411) | 366.0 (1 to 389) |
| All (mild, moderate or severe) asthma exacerbation | 363.0 (2 to 416) | 364.0 (2 to 396) | 361.0 (1 to 411) | 360.0 (1 to 384) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Moderate or severe asthma exacerbation | 365.0 (1 to 416) | | | |
| Severe asthma exacerbation | 366.0 (1 to 416) | | | |
| All (mild, moderate or severe) asthma exacerbation | 278.0 (1 to 416) | | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|----------------------------|---|

Statistical analysis description:

Moderate or severe asthma exacerbation

| | |
|-------------------|--|
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
|-------------------|--|

| | |
|---|-------------------|
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.523 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.15 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.84 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.164 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.06 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.92 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.476 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.16 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|-------------------|
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.85 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.243 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.09 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.027 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.97 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.497 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.12 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 0.84 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|-------------------|
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.126 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.04 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 0.85 |

| | |
|---|--|
| Secondary: Annual rate of asthma exacerbations by exacerbation category | |
| End point title | Annual rate of asthma exacerbations by exacerbation category |
| End point description: The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. | |
| End point type | Secondary |
| End point timeframe: 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|--|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: Exacerbations per year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Moderate or severe asthma exacerbation | 0.46 (0.39 to 0.54) | 0.58 (0.50 to 0.67) | 0.54 (0.47 to 0.63) | 0.67 (0.58 to 0.77) |
| Severe asthma exacerbation | 0.26 (0.22 to 0.31) | 0.38 (0.32 to 0.45) | 0.33 (0.28 to 0.39) | 0.41 (0.35 to 0.48) |
| All (mild, moderate, severe) asthma exacerbation | 0.74 (0.64 to 0.85) | 0.86 (0.75 to 0.98) | 0.93 (0.82 to 1.06) | 0.98 (0.86 to 1.11) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: Exacerbations per year | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Moderate or severe asthma exacerbation | 0.72 (0.63 to 0.82) | | | |
| Severe asthma exacerbation | 0.45 (0.39 to 0.53) | | | |
| All (mild, moderate, severe) asthma exacerbation | 1.23 (1.08 to 1.39) | | | |

Statistical analyses

| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|---|--|
| Statistical analysis description: | |
| Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.12 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.04 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.78 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.17 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.06 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.041 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 0.99 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 0.73 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.531 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.17 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.117 |
| Method | Linear generalized model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.05 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.016 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 0.96 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 0.72 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.161 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.06 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Generalized linear model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.84 |

Secondary: Duration in days of asthma exacerbations by exacerbation category

| | |
|---|---|
| End point title | Duration in days of asthma exacerbations by exacerbation category |
| End point description: The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. | |
| End point type | Secondary |
| End point timeframe: Up to Week 52 | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|--|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Moderate or severe asthma exacerbation | 4.5 (± 10.73) | 5.6 (± 12.87) | 6.7 (± 20.52) | 7.1 (± 17.17) |
| Severe asthma exacerbation | 2.8 (± 7.31) | 4.1 (± 11.18) | 4.9 (± 19.07) | 4.5 (± 10.54) |
| All (mild, moderate, severe) asthma exacerbation | 7.0 (± 16.02) | 8.1 (± 20.51) | 10.7 (± 28.70) | 9.6 (± 21.76) |

| | | | | |
|-------------------------|------------------|--|--|--|
| End point values | Salmeterol/fluti | | | |
|-------------------------|------------------|--|--|--|

| | | | | |
|--|----------------------------|--|--|--|
| | casone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Moderate or severe asthma exacerbation | 8.1 (± 20.63) | | | |
| Severe asthma exacerbation | 5.8 (± 18.24) | | | |
| All (mild, moderate, severe) asthma exacerbation | 12.8 (± 29.21) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.183 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|------------------|
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.155 |
| Method | van Elteren test |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Moderate or severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.007 |
| Method | van Elteren test |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.172 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|------------------|
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.241 |
| Method | van Elteren test |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Severe asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.033 |
| Method | van Elteren test |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | van Elteren test |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|------------------|
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.09 |
| Method | van Elteren test |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: All (mild, moderate, severe) asthma exacerbation | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | van Elteren test |

Secondary: Percentage of participants with at least one asthma exacerbation by exacerbation category

| | |
|---|---|
| End point title | Percentage of participants with at least one asthma exacerbation by exacerbation category |
| End point description: The exacerbation categories were: All (mild, moderate and severe) and combination of moderate or severe and severe. | |
| End point type | Secondary |
| End point timeframe: Up to Week 52 | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|--|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: percentage of participants number (not applicable) | | | | |
| Moderate or severe asthma exacerbation | 30.2 | 32.5 | 31.8 | 35.9 |
| Severe asthma exacerbation | 21.8 | 24.6 | 23.2 | 27.3 |
| All (mild, moderate, severe) asthma exacerbation | 40.2 | 40.2 | 41.9 | 44.0 |

| | | | | |
|------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|------------------|---|--|--|--|

| | | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Moderate or severe asthma exacerbation | 39.7 | | | |
| Severe asthma exacerbation | 29.7 | | | |
| All (mild, moderate, severe) asthma exacerbation | 50.5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time in days to permanent discontinuation of study medication due to asthma exacerbation

| | |
|-----------------|--|
| End point title | Time in days to permanent discontinuation of study medication due to asthma exacerbation |
|-----------------|--|

End point description:

Time from start of treatment until the first event (permanent discontinuation of study medication due to asthma exacerbation) or censoring. Patients without the event were considered as censored at the date of last treatment + 1 day. For patients having the event, the date of the discontinuation of study medication was considered to calculate the time to event.

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

End point timeframe:

52 weeks on average, up to 416 days

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: days | | | | |
| median (full range (min-max)) | 367.0 (11 to 416) | 367.0 (2 to 399) | 367.0 (3 to 411) | 367.0 (2 to 408) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |
| Units: days | | | | |
| median (full range (min-max)) | 367.0 (2 to 416) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.314 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.12 |
| upper limit | 1.96 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1227 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.055 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 1.03 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1223 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.306 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 1.54 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1228 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.566 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 1.94 |

Secondary: Total amount of oral corticosteroid used (in prednisone-equivalent mg doses) to treat asthma exacerbations

| | |
|------------------------|--|
| End point title | Total amount of oral corticosteroid used (in prednisone-equivalent mg doses) to treat asthma exacerbations |
| End point description: | The treatment of asthma exacerbations including the initiation of systemic corticosteroids were done according to investigator's or treating physician's medical judgement and in line with national and international recommendations. If systemic corticosteroids were required, a participant could return to the study after successfully completing a taper of approximately 7-10 days. |
| End point type | Secondary |
| End point timeframe: | Up to Week 52 |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|--|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 615 | 616 | 611 | 607 |
| Units: prednisone-equivalent milligram | | | | |
| arithmetic mean (standard deviation) | 53.4 (± 169.76) | 72.0 (± 211.41) | 73.2 (± 235.90) | 82.5 (± 208.36) |

| End point values | Salmeterol/fluti- casone 50/500 µg b.i.d. | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 612 | | | |

| | | | | |
|--|----------------------|--|--|--|
| Units: prednisone-equivalent milligram | | | | |
| arithmetic mean (standard deviation) | 86.0 (\pm 199.79) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of rescue medication free days over 26 and 52 weeks

| | |
|---|--|
| End point title | Change from baseline in percentage of rescue medication free days over 26 and 52 weeks |
| End point description: All participants were given salbutamol/albuterol to use as rescue medication throughout the study along with e-Diary to record rescue medication use. Rescue medication free days is defined as any day where the participant did not use any puffs of rescue medication during daytime and night-time. | |
| End point type | Secondary |
| End point timeframe: Baseline, 26 weeks, 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 590 | 577 | 578 | 580 |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 22.5 (\pm 1.32) | 19.5 (\pm 1.33) | 23.3 (\pm 1.33) | 18.2 (\pm 1.33) |
| Week 52 | 25.0 (\pm 1.36) | 21.9 (\pm 1.36) | 24.9 (\pm 1.36) | 20.8 (\pm 1.37) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 579 | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | | | | |
| Week 26 | 19.6 (\pm 1.33) | | | |
| Week 52 | 21.8 (\pm 1.36) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.645 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.74 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 6.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.73 |

| | |
|-----------------------------------|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.46 |
| Method | LMM |
| Parameter estimate | LMM |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.1 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.75 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.971 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 3.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.75 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Statistical analysis description: | |
| Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1168 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.963 |
| Method | LMM |
| Parameter estimate | LMM |
| Point estimate | 0.1 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.075 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 6.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.77 |

| | |
|--|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1157 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.517 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.79 |

| | |
|--|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: Week 52 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.956 |
| Method | LMM |
| Parameter estimate | LS Mean |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.78 |

Secondary: Asthma Quality of Life Questionnaire (AQLQ) at Week 52

| | |
|--|--|
| End point title | Asthma Quality of Life Questionnaire (AQLQ) at Week 52 |
| End point description: AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma, with a recall time of two weeks and each question to be answered on a 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains: - Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items) - Activity limitation = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items) - Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items) - Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items) - Overall Score = Mean of Items 1 to 32 (32 items) The overall AQLQ score reported below is the mean of all 32 responses and ranges from 1 to 7, where higher scores indicate better quality of life. | |
| End point type | Secondary |
| End point timeframe: 52 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-------------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 606 | 593 | 595 | 599 |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 5.555 (± 0.0354) | 5.445 (± 0.0358) | 5.535 (± 0.0356) | 5.499 (± 0.0358) |

| | | | | |
|-------------------------------------|---|--|--|--|
| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 594 | | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 5.495 (± 0.0357) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1201 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.69 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.078 |
| upper limit | 0.118 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0502 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1200 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.232 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.038 |
| upper limit | 0.159 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0502 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.285 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.054 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.153 |
| upper limit | 0.045 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0506 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1187 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.319 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | -0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.049 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0505 |

Secondary: Pre-dose FEV1 at weeks 4 and 12

| | |
|-----------------|---------------------------------|
| End point title | Pre-dose FEV1 at weeks 4 and 12 |
|-----------------|---------------------------------|

End point description:

Pre-dose FEV1 is defined as average of the two FEV1 measurements taken 45 min and 15 min pre evening dose. It was assessed by performing spirometric assessment. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 4 weeks, 12 weeks | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|---|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 606 | 594 | 592 | 596 |
| Units: litres | | | | |
| least squares mean (standard deviation) | | | | |
| Week 4 | 2.032 (± 0.0122) | 1.983 (± 0.0123) | 1.963 (± 0.0124) | 1.950 (± 0.0123) |
| Week 12 | 2.024 (± 0.0134) | 1.994 (± 0.0135) | 1.966 (± 0.0135) | 1.944 (± 0.0136) |

| End point values | Salmeterol/fluticasone 50/500 µg b.i.d. | | | |
|---|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 598 | | | |
| Units: litres | | | | |
| least squares mean (standard deviation) | | | | |
| Week 4 | 1.887 (± 0.0123) | | | |
| Week 12 | 1.907 (± 0.0135) | | | |

Statistical analyses

| Statistical analysis title | QVM149 150/50/160 µg vs QMF149 150/320 µg |
|---|--|
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.068 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.036 |
| upper limit | 0.101 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0166 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/160 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.145 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.113 |
| upper limit | 0.177 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0165 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.033 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.066 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0167 |

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

Week 4

| | |
|---|--|
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.096 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.064 |
| upper limit | 0.129 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0166 |

Statistical analysis title

QVM149 150/50/160 µg vs QMF149 150/320 µg

Statistical analysis description:

Week 12

| | |
|---|--|
| Comparison groups | QVM149 150/50/160 µg o.d. v QMF149 150/320 µg o.d. |
| Number of subjects included in analysis | 1198 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.058 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.022 |
| upper limit | 0.094 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0184 |

Statistical analysis title

QVM149 150/50/160 µg vs S/F 50/500 µg

Statistical analysis description:

Week 12

| | |
|-------------------|---|
| Comparison groups | QVM149 150/50/160 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
|-------------------|---|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.117 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.081 |
| upper limit | 0.153 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0183 |

| | |
|---|---|
| Statistical analysis title | QVM149 150/50/80 µg vs QMF149 150/160 µg |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v QMF149 150/160 µg o.d. |
| Number of subjects included in analysis | 1190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.007 |
| Method | MMRM |
| Parameter estimate | LS Mean |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.013 |
| upper limit | 0.086 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0185 |

| | |
|---|--|
| Statistical analysis title | QVM149 150/50/80 µg vs S/F 50/500 µg |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | QVM149 150/50/80 µg o.d. v Salmeterol/fluticasone 50/500 µg b.i.d. |
| Number of subjects included in analysis | 1192 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |
| Parameter estimate | MMRM |
| Point estimate | 0.087 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.051 |
| upper limit | 0.123 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0184 |

Secondary: Percentage of participants with composite endpoint of serious asthma outcomes

| | |
|--|---|
| End point title | Percentage of participants with composite endpoint of serious asthma outcomes |
| End point description: A composite endpoint of serious asthma outcomes is defined as asthma-related hospitalization, asthma-related intubation, or asthma-related death and was reviewed by the Adjudication Committee. | |
| End point type | Secondary |
| End point timeframe: Up to Week 52 | |

| End point values | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. | QMF149 150/160 µg o.d. |
|-----------------------------------|---------------------------------|--------------------------------|------------------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 616 | 617 | 613 | 608 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 1.4 | 2.5 | 1.9 | 1.6 |

| End point values | Salmeterol/fluti casone 50/500 µg b.i.d. | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 618 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 1.2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days (52 weeks on average, up to 416 days).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "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 | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | QVM149 150/50/160 µg o.d. |
|-----------------------|---------------------------|

Reporting group description:

QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|-----------------------|--------------------------|
| Reporting group title | QVM149 150/50/80 µg o.d. |
|-----------------------|--------------------------|

Reporting group description:

QVM149 150/50/80 µg (indacaterol acetate/glycopyrronium/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|-----------------------|------------------------|
| Reporting group title | QMF149 150/320 µg o.d. |
|-----------------------|------------------------|

Reporting group description:

QMF149 150/320 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|-----------------------|------------------------|
| Reporting group title | QMF149 150/160 µg o.d. |
|-----------------------|------------------------|

Reporting group description:

QMF149 150/160 µg (indacaterol acetate/mometasone furoate) once daily (o.d.) delivered via Concept1 device

| | |
|-----------------------|---|
| Reporting group title | Salmeterol/fluticasone 50/500 µg b.i.d. |
|-----------------------|---|

Reporting group description:

Salmeterol xinafoate /fluticasone propionate 50/500 µg twice daily (b.i.d.) delivered via Accuhaler®

| Serious adverse events | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. |
|---|------------------------------|-----------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 616 (7.47%) | 49 / 617 (7.94%) | 52 / 613 (8.48%) |
| number of deaths (all causes) | 2 | 1 | 4 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central nervous system lymphoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liposarcoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian adenoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salivary gland adenoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue sarcoma | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Angiopathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Aortic dissection rupture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 616 (0.32%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 2 / 617 (0.32%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose vein | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 616 (0.32%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 616 (0.32%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcoidosis | | | |

| | | | |
|---|-----------------|------------------|------------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Cystocele | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 9 / 616 (1.46%) | 15 / 617 (2.43%) | 12 / 613 (1.96%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 20 | 1 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cough | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 2 / 617 (0.32%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal septum deviation | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 3 / 613 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Sinus polyp | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sleep apnoea syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 2 / 613 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 2 / 617 (0.32%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Foot fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural discomfort | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute cardiac event | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Alcoholic seizure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic neuropathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 616 (0.32%) | 1 / 617 (0.16%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Middle ear effusion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otorrhoea | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 2 / 613 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Enteritis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 2 / 613 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal angiodysplasia | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneal adhesions | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctitis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal polyp | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 3 / 616 (0.49%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Primary biliary cholangitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Steatohepatitis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephritis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw disorder | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal deformity | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HIV infection | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 1 / 617 (0.16%) | 3 / 613 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mastoiditis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media chronic | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 616 (0.49%) | 2 / 617 (0.32%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salpingitis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 1 / 617 (0.16%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 1 / 613 (0.16%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 616 (0.32%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 616 (0.16%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 616 (0.00%) | 0 / 617 (0.00%) | 0 / 613 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | QMF149 150/160 µg o.d. | Salmeterol/fluticasone 50/500 µg b.i.d. | |
|---|---------------------------|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 38 / 608 (6.25%) | 39 / 618 (6.31%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system lymphoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liposarcoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian adenoma | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (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 | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salivary gland adenoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue sarcoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Angiopathy | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic dissection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic dissection rupture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic vasculitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (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 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Cystocele | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 8 / 608 (1.32%) | 9 / 618 (1.46%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus polyp | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 2 / 608 (0.33%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural discomfort | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin abrasion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute cardiac event | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (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 / 608 (0.16%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 608 (0.33%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Alcoholic seizure | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic neuropathy | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient global amnesia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Middle ear effusion | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otorrhoea | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal angiodysplasia | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritoneal adhesions | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal polyp | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 2 / 608 (0.33%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Primary biliary cholangitis | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Steatohepatitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 2 / 618 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus urethral | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw disorder | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 608 (0.33%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal deformity | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 2 / 618 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 2 / 618 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 2 / 608 (0.33%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HIV infection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (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 | 1 / 608 (0.16%) | 2 / 618 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media chronic | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 608 (0.49%) | 5 / 618 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salpingitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 608 (0.16%) | 0 / 618 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 608 (0.00%) | 1 / 618 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | QVM149 150/50/160 µg o.d. | QVM149 150/50/80 µg o.d. | QMF149 150/320 µg o.d. |
|---|------------------------------|-----------------------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 367 / 616 (59.58%) | 387 / 617 (62.72%) | 377 / 613 (61.50%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 16 / 616 (2.60%) | 19 / 617 (3.08%) | 14 / 613 (2.28%) |
| occurrences (all) | 20 | 20 | 17 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 23 / 616 (3.73%) | 30 / 617 (4.86%) | 24 / 613 (3.92%) |
| occurrences (all) | 32 | 32 | 27 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 616 (2.76%) | 11 / 617 (1.78%) | 10 / 613 (1.63%) |
| occurrences (all) | 23 | 11 | 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 243 / 616 (39.45%) | 242 / 617 (39.22%) | 249 / 613 (40.62%) |
| occurrences (all) | 436 | 476 | 539 |
| Cough | | | |
| subjects affected / exposed | 24 / 616 (3.90%) | 18 / 617 (2.92%) | 11 / 613 (1.79%) |
| occurrences (all) | 28 | 21 | 11 |
| Dysphonia | | | |

| | | | |
|---|-------------------------|--------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 24 / 616 (3.90%) 26 | 13 / 617 (2.11%) 13 | 10 / 613 (1.63%) 12 |
| Rhinitis allergic subjects affected / exposed occurrences (all) | 19 / 616 (3.08%) 22 | 17 / 617 (2.76%) 19 | 9 / 613 (1.47%) 11 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 616 (0.32%) 2 | 14 / 617 (2.27%) 15 | 5 / 613 (0.82%) 5 |
| Back pain subjects affected / exposed occurrences (all) | 12 / 616 (1.95%) 13 | 18 / 617 (2.92%) 20 | 18 / 613 (2.94%) 20 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 49 / 616 (7.95%) 68 | 48 / 617 (7.78%) 65 | 46 / 613 (7.50%) 51 |
| Influenza subjects affected / exposed occurrences (all) | 19 / 616 (3.08%) 24 | 21 / 617 (3.40%) 26 | 23 / 613 (3.75%) 25 |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 13 / 616 (2.11%) 18 | 12 / 617 (1.94%) 13 | 12 / 613 (1.96%) 14 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 64 / 616 (10.39%) 82 | 76 / 617 (12.32%) 101 | 73 / 613 (11.91%) 93 |
| Pharyngitis subjects affected / exposed occurrences (all) | 22 / 616 (3.57%) 26 | 21 / 617 (3.40%) 21 | 20 / 613 (3.26%) 22 |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 18 / 616 (2.92%) 23 | 17 / 617 (2.76%) 24 | 11 / 613 (1.79%) 16 |
| Rhinitis subjects affected / exposed occurrences (all) | 12 / 616 (1.95%) 16 | 20 / 617 (3.24%) 23 | 17 / 613 (2.77%) 19 |
| Sinusitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 14 / 616 (2.27%) | 18 / 617 (2.92%) | 9 / 613 (1.47%) |
| occurrences (all) | 15 | 20 | 10 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 33 / 616 (5.36%) | 45 / 617 (7.29%) | 52 / 613 (8.48%) |
| occurrences (all) | 46 | 60 | 66 |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 17 / 616 (2.76%) | 22 / 617 (3.57%) | 27 / 613 (4.40%) |
| occurrences (all) | 18 | 26 | 32 |
| Urinary tract infection | | | |
| subjects affected / exposed | 8 / 616 (1.30%) | 5 / 617 (0.81%) | 10 / 613 (1.63%) |
| occurrences (all) | 9 | 5 | 10 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 21 / 616 (3.41%) | 31 / 617 (5.02%) | 38 / 613 (6.20%) |
| occurrences (all) | 21 | 37 | 49 |

| Non-serious adverse events | QMF149 150/160 µg o.d. | Salmeterol/fluticasone 50/500 µg b.i.d. | |
|---|------------------------|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 392 / 608 (64.47%) | 419 / 618 (67.80%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 17 / 608 (2.80%) | 23 / 618 (3.72%) | |
| occurrences (all) | 19 | 27 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 34 / 608 (5.59%) | 25 / 618 (4.05%) | |
| occurrences (all) | 44 | 35 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 608 (1.64%) | 15 / 618 (2.43%) | |
| occurrences (all) | 12 | 20 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 265 / 608 (43.59%) | 306 / 618 (49.51%) | |
| occurrences (all) | 574 | 710 | |
| Cough | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 14 / 608 (2.30%) | 15 / 618 (2.43%) | |
| occurrences (all) | 16 | 19 | |
| Dysphonia | | | |
| subjects affected / exposed | 9 / 608 (1.48%) | 12 / 618 (1.94%) | |
| occurrences (all) | 9 | 12 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 15 / 608 (2.47%) | 20 / 618 (3.24%) | |
| occurrences (all) | 19 | 26 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 12 / 608 (1.97%) | 10 / 618 (1.62%) | |
| occurrences (all) | 12 | 10 | |
| Back pain | | | |
| subjects affected / exposed | 16 / 608 (2.63%) | 14 / 618 (2.27%) | |
| occurrences (all) | 19 | 14 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 44 / 608 (7.24%) | 55 / 618 (8.90%) | |
| occurrences (all) | 58 | 70 | |
| Influenza | | | |
| subjects affected / exposed | 26 / 608 (4.28%) | 25 / 618 (4.05%) | |
| occurrences (all) | 30 | 30 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 17 / 608 (2.80%) | 22 / 618 (3.56%) | |
| occurrences (all) | 22 | 27 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 64 / 608 (10.53%) | 83 / 618 (13.43%) | |
| occurrences (all) | 90 | 117 | |
| Pharyngitis | | | |
| subjects affected / exposed | 19 / 608 (3.13%) | 20 / 618 (3.24%) | |
| occurrences (all) | 19 | 23 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 29 / 608 (4.77%) | 22 / 618 (3.56%) | |
| occurrences (all) | 38 | 29 | |
| Rhinitis | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 20 / 608 (3.29%) | 11 / 618 (1.78%) | |
| occurrences (all) | 20 | 13 | |
| Sinusitis | | | |
| subjects affected / exposed | 17 / 608 (2.80%) | 14 / 618 (2.27%) | |
| occurrences (all) | 22 | 14 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 48 / 608 (7.89%) | 52 / 618 (8.41%) | |
| occurrences (all) | 65 | 66 | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 28 / 608 (4.61%) | 29 / 618 (4.69%) | |
| occurrences (all) | 31 | 33 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 9 / 608 (1.48%) | 13 / 618 (2.10%) | |
| occurrences (all) | 10 | 16 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 26 / 608 (4.28%) | 47 / 618 (7.61%) | |
| occurrences (all) | 30 | 61 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 03 August 2015 | Amendment 1 added the validated method for collecting data for the ACQ-7 instrument. The changes were: Questions 1-6 of the ACQ-7 to be completed by patients based on one week recall. Item 7 to be completed by the Investigator using the MasterScope spirometer at the study site. Derivation of rescue medication from the e-diary (6th item on ACQ-7) was not to be performed. |
| 31 August 2015 | Appendix 1 and 5 were replaced. Appendix 1: Instruction for use of Concept1 (picture 3 and 5 were missing and a black field was covering the text describing Concept1 picture). Appendix 5 - AQLQ-S (questions 26-31 of the questionnaire were missing and the page was blank and a black field was covering part of the question 32) which were incomplete due to a technical issue during protocol publication. Updated: additional pregnancy testing requirements, and spirometry assessment method not to include reversibility test. |
| 08 October 2015 | Modified the ACQ score inclusion criteria from $ACQ \geq 2$ to $ACQ \geq 1.5$ based on recent feedback from an external expert advisory board in September 2015. Initial threshold of ≥ 2 was defined based on internal modelling and simulation data as well as published literature (Barnes et al 2014). However, expert advisory board members suggested that a threshold of 1.5 is more clinically meaningful for this patient population. Asthma worsening criteria was updated and relevant sections such as protocol summary rationale for dosing and supportive analysis. |
| 08 September 2016 | After approval of tiotropium Respimat 5 µg o.d. for asthma in September 2014, changes to GINA guidelines in 2015 were expected to result in a progressive increase in use of tiotropium (LAMA) as add on to ICS/LABA therapy in GINA \geq Step 4 patients. The Amendment reduced the exclusion period for LAMA use from 12 months to 3 months prior to Visit 1. This broadened the pool of eligible patients and help better reflect rapidly evolving medical practice in GINA Step ≥ 4 asthma patients eDiary alert handling during the Run-In Epoch due to asthma worsening was updated. |
| 08 February 2017 | A modification was made of the inclusion criteria for the duration of baseline LABA/ICS requirements from 1 year to 3 months. Revision of the sample size based on the re-estimation of the drop-out rate at Week 26 when the primary and key secondary objectives are evaluated. |
| 18 December 2017 | Primary analysis to be conducted after all patients have completed at least 26 weeks treatment (Visit 207). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported