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	v2
This version publication date	07 August 2020
First version publication date	28 June 2020
Version creation reason	

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	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	United Kingdom: 9
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	Jordan: 7
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
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	Vietnam: 28
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	Subject, Investigator, Data analyst, Assessor

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	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	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/fluticasone 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/fluticasone 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 Week 12	2.952 (± 0.0163) 2.965 (± 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/fluticasone 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/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 (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 modeñ
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/fluticasone 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 (± 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 (± 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	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/fluticasone 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:	
Any signs or symptoms that occurs during study treatment plus the 30 days post treatment.	
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	24 / 616 (3.90%)	13 / 617 (2.11%)	10 / 613 (1.63%)
occurrences (all)	26	13	12
Rhinitis allergic			
subjects affected / exposed	19 / 616 (3.08%)	17 / 617 (2.76%)	9 / 613 (1.47%)
occurrences (all)	22	19	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 616 (0.32%)	14 / 617 (2.27%)	5 / 613 (0.82%)
occurrences (all)	2	15	5
Back pain			
subjects affected / exposed	12 / 616 (1.95%)	18 / 617 (2.92%)	18 / 613 (2.94%)
occurrences (all)	13	20	20
Infections and infestations			
Bronchitis			
subjects affected / exposed	49 / 616 (7.95%)	48 / 617 (7.78%)	46 / 613 (7.50%)
occurrences (all)	68	65	51
Influenza			
subjects affected / exposed	19 / 616 (3.08%)	21 / 617 (3.40%)	23 / 613 (3.75%)
occurrences (all)	24	26	25
Lower respiratory tract infection			
subjects affected / exposed	13 / 616 (2.11%)	12 / 617 (1.94%)	12 / 613 (1.96%)
occurrences (all)	18	13	14
Nasopharyngitis			
subjects affected / exposed	64 / 616 (10.39%)	76 / 617 (12.32%)	73 / 613 (11.91%)
occurrences (all)	82	101	93
Pharyngitis			
subjects affected / exposed	22 / 616 (3.57%)	21 / 617 (3.40%)	20 / 613 (3.26%)
occurrences (all)	26	21	22
Respiratory tract infection viral			
subjects affected / exposed	18 / 616 (2.92%)	17 / 617 (2.76%)	11 / 613 (1.79%)
occurrences (all)	23	24	16
Rhinitis			
subjects affected / exposed	12 / 616 (1.95%)	20 / 617 (3.24%)	17 / 613 (2.77%)
occurrences (all)	16	23	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 ≥ 2 to ACQ ≥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 ≥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