Clinical trial results:
A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma

Summary

EudraCT number	2017-000136-34
Trial protocol	CZ HU GR PL ES SK
Global end of trial date	19 July 2019

Results information

Result version number	v2 (current)
This version publication date	13 June 2021
First version publication date	31 July 2020
Version creation reason	• Correction of full data set Additional text added in the field Adverse Events reporting additional description.

Trial information

Trial identification

Sponsor protocol code	CQVM149B2306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03158311
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	19 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to demonstrate non-inferiority of either QVM149 high-dose (150/50/160 µg) or QVM149 medium-dose (150/50/80 µg) to comparator salmeterol/fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire (AQLQ) after 24 weeks of treatment in uncontrolled moderate to severe asthmatics patients.

Protection of trial subjects:

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

At Visit 1, all patients were provided with a short acting β2-agonist (100 µg salbutamol MDI or equivalent albuterol MDI) which they were instructed to use throughout the study as rescue medication. Nebulized salbutamol was not allowed as rescue medication throughout the entire trial. No other rescue treatment was permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	South Africa: 47
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Turkey: 25
Country: Number of subjects enrolled	Vietnam: 16
Country: Number of subjects enrolled	Argentina: 412
Country: Number of subjects enrolled	Chile: 27
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Czech Republic: 54
Country: Number of subjects enrolled	Germany: 213
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Hungary: 99
Country: Number of subjects enrolled	India: 73

Country: Number of subjects enrolled	Israel: 45
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Peru: 27
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 217
Country: Number of subjects enrolled	Serbia: 56
Worldwide total number of subjects	1426
EEA total number of subjects	449

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)	1137
From 65 to 84 years	289
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 166 investigative sites in 20 countries from 05 Feb 2018 to 19 Jul 2019.

Pre-assignment

Screening details:

A total of 1917 participants were screened. A 2 week run-in phase preceded the randomized treatment phase of the study. 1821 participants entered the run-in phase. Those participants who met the inclusion criteria entered the randomized treatment phase. Participants were randomized with a randomization ratio of 1:1:1 to three treatment arms.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	QVM149 150/50/80 µg

Arm description:

QVM149 150/50/80 µg o.d. delivered via Concept1

Arm type	Experimental
Investigational medicinal product name	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:

QVM149 150/50/80 µg once daily delivered via Concept1

Arm title	QVM149 150/50/160 µg

Arm description:

QVM149 150/50/160 µg o.d. delivered via Concept1

Arm type	Experimental
Investigational medicinal product name	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:

QVM149 150/50/160 µg once daily delivered via Concept1

Arm title	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Arm description:

Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®

Arm type	Active comparator

Investigational medicinal product name	Salmeterol/flucticasone plus tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Salmeterol/fluticasone 50/500 µg twice daily delivered via Accuhaler® plus tiotropium 5 µg once daily delivered via Respimat®.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The free triple combination of salmeterol/fluticasone + tiotropium was open label. Within the two QVM149 treatment arms patients, investigator staff, and persons performing the assessments, remained blind to the identity of the actual QVM149 treatment dose but had knowledge that the patient had been assigned QVM149 as study treatment. The data analysts and sponsor team were blinded

Number of subjects in period 1	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Started	474	476	476
Full Analysis Set (FAS)	474	476	475
Safety Set (SAF)	474	476	475
Completed	452	460	448
Not completed	22	16	28
Physician decision	2	3	7
Techinical Problems	3	1	5
Adverse event, non-fatal	5	3	3
Randomized but not treated	-	-	1
Pregnancy	-	2	-
Subject/Guardian Decision	10	6	11
Study Terminated by Sponsor	1	-	-
Lost to follow-up	1	1	1

Baseline characteristics

Reporting groups	
Reporting group title	QVM149 150/50/80 µg
Reporting group description:	
QVM149 150/50/80 µg o.d. delivered via Concept1	
Reporting group title	QVM149 150/50/160 µg
Reporting group description:	
QVM149 150/50/160 µg o.d. delivered via Concept1	
Reporting group title	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Reporting group description:	
Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®	

Reporting group values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects	474	476	476
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)	381	375	381
From 65-84 years	93	101	95
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.9	52.7	53.1
standard deviation	± 13.58	± 13.34	± 13.08
Sex: Female, Male Units: Participants			
Female	306	289	307
Male	168	187	169
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	5	1	10
Asian	36	34	33
Black or African American	6	5	3
White	401	392	391
Other	26	44	39

Reporting group values	Total		
Number of subjects	1426		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	1137		
From 65-84 years	289		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	902		
Male	524		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	16		
Asian	103		
Black or African American	14		
White	1184		
Other	109		

End points

End points reporting groups

Reporting group title	QVM149 150/50/80 µg
Reporting group description: QVM149 150/50/80 µg o.d. delivered via Concept1	
Reporting group title	QVM149 150/50/160 µg
Reporting group description: QVM149 150/50/160 µg o.d. delivered via Concept1	
Reporting group title	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Reporting group description: Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®	

Primary: Change from Baseline in Asthma Quality of Life Questionnaire (AQLQ) Total Score

End point title	Change from Baseline in Asthma Quality of Life Questionnaire (AQLQ) Total Score
End point description: The AQLQ is a 32-item asthma 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, where 1=totally limited/problems all the time and 7= not at all limited/no problems. It consists of 4 domains: symptoms, activity limitation, emotional funtion, and emotional stimuli. The overall score is calculated as the mean of 32 items. Higher AQLQ scores indicate better health-related quality of life.	
End point type	Primary
End point timeframe: Baseline and Week 24	

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	436	453	435	
Units: Score on a scale				
least squares mean (standard error)	0.715 (± 0.070)	0.827 (± 0.069)	0.753 (± 0.069)	

Statistical analyses

Statistical analysis title	AQLQ: QVM149 150/50/80 µg vs Active comparator
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Number of subjects included in analysis	871
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square mean (LS Mean)
Point estimate	-0.038
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.139
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

[1] - Non-inferiority margin: 0.25 points

[2] - P-Value is one-sided

Statistical analysis title	AQLQ: QVM149 150/50/1600 µg vs Active Comparator
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.073
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.027
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

[3] - Non-inferiority margin: 0.25 points

[4] - P-Value is one-sided

Secondary: Change from Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change from Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1)

End point description:

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. Trough FEV1 is the mean of two FEV1 values measures taken 15 minutes (min) and 45 min prior to evening dose.

End point type	Secondary

End point timeframe:

Baseline, Week 8, Week 16 and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	420	438	425	
Units: Litre (L)				
least squares mean (standard error)				
Week 8 (Number analyzed: 382/395/371)	0.246 (± 0.020)	0.309 (± 0.020)	0.243 (± 0.020)	
Week 16 (Number analyzed: 357/389/371)	0.251 (± 0.020)	0.319 (± 0.020)	0.253 (± 0.020)	
Week 24 (Number analyzed: 367/385/372)	0.248 (± 0.021)	0.334 (± 0.021)	0.238 (± 0.021)	

Statistical analyses

Statistical analysis title	FEV1:QVM149 150/50/80µg vs Active Comparator
Statistical analysis description: Week 8	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.892 [5]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.052
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:
[5] - P-value is two-sided

Statistical analysis title	FEV1: QVM149 150/50/160 µg vs Active Comparator
Statistical analysis description: Week 8	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [6]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.067

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[6] - P-value is two-sided

Statistical analysis title	FEV1: QVM149 150/50/80 µg vs Active Comparator

Statistical analysis description:

Week 16

Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.945 [7]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[7] - P-value is two-sided

Statistical analysis title	FEV1: QVM149 150/50/160 µg vs Active Comparator

Statistical analysis description:

Week 16

Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [8]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.114
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:
[8] - P-value is two-sided

Statistical analysis title	FEV1: QVM149 150/50/80 µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.713 [9]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.026

Notes:
[9] - P-value is two-sided

Statistical analysis title	FEV1: QVM149 150/50/160 µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.026

Notes:
[10] - P-value is two-sided

Secondary: Change from Baseline in Asthma Control Questionnaire (ACQ-7) Total Score

End point title	Change from Baseline in Asthma Control Questionnaire (ACQ-7) Total Score

End point description:

The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue medication use and 1 on airway calibre (FEV1 % predicted). All seven items are scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating poor control. The questions are equally weighted and the total score is the mean of the seven items. Higher score indicates worst symptoms. The first 6 questions of the ACQ-7 were completed by the participant while the last question was completed by the study investigator using data from the Master Scope spirometer. A negative change from baseline indicates improvement in lung function.

End point type	Secondary

End point timeframe:

Baseline, Week 16 and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	447	454	447	
Units: Score on a scale				
least squares mean (standard error)				
Week 16 (Number analyzed: 436/441/428)	-1.043 (± 0.045)	-1.098 (± 0.045)	-1.020 (± 0.045)	
Week 24 (Number analyzed: 437/452/436)	-1.080 (± 0.046)	-1.172 (± 0.045)	-1.048 (± 0.046)	

Statistical analyses

Statistical analysis title	ACQ-7: QVM149 150/50/80 µg vs Active Comparator

Statistical analysis description:

Week 16

Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	894
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 [11]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[11] - P-value is one-sided

Statistical analysis title	ACQ-7: QVM149 150/50/160 µg vs Active Comparator
Statistical analysis description:	
Week 16	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 [12]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.169
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[12] - P-value is one-sided

Statistical analysis title	ACQ-7: QVM149 150/50/80 µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	894
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245 [13]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.125
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[13] - P-value is one sided

Statistical analysis title	ACQ-7: QVM149 150/50/160 µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [14]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.216
upper limit	-0.032
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[14] - P-value is one sided

Secondary: Change from Baseline in AQLQ Total Score

End point title	Change from Baseline in AQLQ Total Score

End point description:

The AQLQ is a 32-item asthma 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, where 1=totally limited/problems all the time and 7= not at all limited/no problems. It consists of 4 domains: symptoms, activity limitation, emotional function and environmental stimuli. The overall score is calculated as the mean of 32 items. Higher AQLQ scores indicate better health-related quality of life.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	435	442	429	
Units: Score on a scale				
least squares mean (standard error)	0.690 (± 0.069)	0.755 (± 0.068)	0.673 (± 0.069)	

Statistical analyses

Statistical analysis title	AQLQ: QVM149 150/50/80 µg vs Active Comparator
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.719 [15]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.079
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[15] - P-value is two-sided

Statistical analysis title	AQLQ: QVM149 150/50/160 µg vs Active Comparator
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	871
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 [16]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.179
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[16] - P-value is two-sided

Secondary: Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Decrease from Baseline ACQ-7 ≥ 0.5

End point title	Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Decrease from Baseline ACQ-7 ≥ 0.5

End point description:

The ACQ-7 measured asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue medication use and 1 on airway calibre (FEV1 % predicted). All seven items are scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating poor control. The questions are equally weighted and the total score is the mean of the seven items. Higher score indicates worst symptoms. The first 6 questions of the ACQ-7 were completed by the participant while the last question was completed by the study investigator using data from the Master Scope spirometer. A negative change from baseline indicates improvement in lung function. Decrease of ACQ-7 score of at least 0.5 from baseline was considered clinically meaningful.

End point type	Secondary

End point timeframe:
Baseline and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	447	454	447	
Units: Percentage of participants				
number (not applicable)	87.9	85.2	83.9	

Statistical analyses

Statistical analysis title	MCID ACQ-7:QVM149 150/50/80µg vs Active Comparator
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	894
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.61

Notes:

[17] - P-value is one sided

Statistical analysis title	MCID ACQ-7:QVM149 150/50/160µg vsActive Comparator
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	901
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.227 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.46

Notes:

[18] - P-value is one-sided

Secondary: Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Change from baseline AQLQ ≥ 0.5

End point title	Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Change from baseline AQLQ ≥ 0.5

End point description:

The AQLQ is a 32-item asthma 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, where 1=totally limited/problems all the time and 7= not at all limited/no problems. It consists of 4 domains: symptoms, activity limitation, emotional function and environmental stimuli. The overall score is calculated as the mean of 32 items. Higher AQLQ scores indicate better health-related quality of life. An improvement of 0.5 points in AQLQ score is considered to be the minimally clinically important difference in asthma.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	444	454	441	
Units: Percentage of participants				
number (not applicable)	71.6	73.3	67.8	

Statistical analyses

Statistical analysis title	MCID AQLQ: QVM149 150/50/80µg vs Active Comparator
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.49

Notes:

[19] - P-value is one sided

	MCID AQLQ:QVM149 150/50/160µg vs Active Comparator

Statistical analysis title	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	895
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.7

Notes:

[20] - P-Value is one sided

Secondary: Change from Baseline in Forced Vital Capacity (FVC)	
End point title	Change from Baseline in Forced Vital Capacity (FVC)

End point description:

FVC is the total volume of air exhaled during a expiratory maneuvre. It was assessed by performing a spirometry assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8, Week 16 and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	420	438	425	
Units: Litre (L)				
least squares mean (standard error)				
Week 8 (Number analyzed: 382/395/371)	0.216 (± 0.021)	0.272 (± 0.021)	0.219 (± 0.021)	
Week 16 (Number analyzed: 357/389/371)	0.221 (± 0.021)	0.275 (± 0.021)	0.217 (± 0.021)	
Week 24 (Number analyzed: 367/385/372)	0.214 (± 0.022)	0.280 (± 0.022)	0.186 (± 0.022)	

Statistical analyses

Statistical analysis title	FVC: QVM149 150/50/80µg vs Active Comparator

Statistical analysis description:

Week 8

Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus

	tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.908 [21]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.049
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[21] - P-Value is two-sided

Statistical analysis title	FVC: QVM149 150/50/160µg vs Active Comparator
Statistical analysis description:	
Week 8	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [22]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.104
Variability estimate	Standard error of the mean
Dispersion value	0.026

Notes:

[22] - P-Value is two-sided

Statistical analysis title	FVC: QVM149 150/50/80µg vs Active Comparator
Statistical analysis description:	
Week 16	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87 [23]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.026

Notes:

[23] - P-Value is two-sided

Statistical analysis title	FVC: QVM149 150/50/160µg vs Active Comparator
Statistical analysis description:	
Week 16	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [24]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.109
Variability estimate	Standard error of the mean
Dispersion value	0.026

Notes:

[24] - P-Value is two-sided

Statistical analysis title	FVC: QVM149 150/50/80µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.303 [25]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.028

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[25] - P-Value is two-sided

Statistical analysis title	FVC: QVM149 150/50/160µg vs Active Comparator

Statistical analysis description:

Week 24

Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [26]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.148
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[26] - P-Value is two-sided

Secondary: Change from Baseline in Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF25-75)

End point title	Change from Baseline in Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF25-75)

End point description:

Forced expiratory flow during the mid (25 - 75%) portion of the FVC. It was assessed by performing spirometric assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 8, Week 16 and Week 24

End point values	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	420	438	425	
Units: Litres/second (L/s)				
least squares mean (standard error)				
Week 8 (Number analyzed: 382/395/371)	0.290 (± 0.027)	0.332 (± 0.027)	0.270 (± 0.027)	
Week 16 (Number analyzed: 357/389/371)	0.291 (± 0.028)	0.355 (± 0.027)	0.297 (± 0.027)	
Week 24 (Number analyzed: 367/385/372)	0.290 (± 0.028)	0.375 (± 0.028)	0.286 (± 0.028)	

Statistical analyses

Statistical analysis title	FEF25-75:QVM149 150/50/80µg vs Active Comparator
Statistical analysis description: Week 8	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.563 [27]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.087
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:
[27] - P-value is two-sided

Statistical analysis title	FEF25-75:QVM149 150/50/160µg vs Active Comparator
Statistical analysis description: Week 8	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [28]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.062

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.129
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[28] - P-Value is two-sided

Statistical analysis title	FEF25-75:QVM149 150/50/80µg vs Active Comparator

Statistical analysis description:

Week 16

Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.844 [29]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.062
Variability estimate	Standard error of the mean
Dispersion value	0.035

Notes:

[29] - P-Value is two-sided

Statistical analysis title	FEF25-75:QVM149 150/50/160µg vs Active Comparator

Statistical analysis description:

Week 16

Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 [30]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.035

Notes:
[30] - P-Value is two-sided

Statistical analysis title	FEF25-75:QVM149 150/50/80µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/80 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927 [31]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.074
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:
[31] - P-Value is two-sided

Statistical analysis title	FEF25-75:QVM149 150/50/160µg vs Active Comparator
Statistical analysis description:	
Week 24	
Comparison groups	QVM149 150/50/160 µg v Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [32]
Method	MMRM
Parameter estimate	LS Mean
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.159
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:
[32] - P-Value is two-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected starting on or after the time of first administration of study drug but not later than 7 days (30 days in case of a Serious Adverse Events) after the last administration.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	QVM149 150/50/80µg

Reporting group description:

QVM149 150/50/80 µg o.d. delivered via Concept1

Reporting group title	QVM149 150/50/160µg

Reporting group description:

QVM149 150/50/160 µg o.d. delivered via Concept1

Reporting group title	Salmeterol/fluticasone 50/500µg plus tiotropium 5µg

Reporting group description:

Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®

Serious adverse events	QVM149 150/50/80µg	QVM149 150/50/160µg	Salmeterol/fluticasone 50/500µg plus tiotropium 5µg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 474 (2.95%)	18 / 476 (3.78%)	19 / 475 (4.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Fibroadenoma of breast			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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 benign neoplasm			

subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract neoplasm			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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			
Deep vein thrombosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Thrombophlebitis superficial			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Asthma			
subjects affected / exposed	4 / 474 (0.84%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Hypoxia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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			
Contusion			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Intentional product misuse			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	2 / 475 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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

Wrist fracture			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Myocardial infarction			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Tachycardia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Polyneuropathy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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 polyp			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
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	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Cholecystitis acute			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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			
Atypical pneumonia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Bronchiolitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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 viral			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Lung infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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
Pilonidal cyst			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (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
Pneumonia			
subjects affected / exposed	0 / 474 (0.00%)	5 / 476 (1.05%)	0 / 475 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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 abscess			

subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (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

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

Non-serious adverse events	QVM149 150/50/80µg	QVM149 150/50/160µg	Salmeterol/fluticasone 50/500µg plus tiotropium 5µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	245 / 474 (51.69%)	246 / 476 (51.68%)	241 / 475 (50.74%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Prostatic adenoma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Respiratory tract neoplasm			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Uterine leiomyoma			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	7 / 474 (1.48%)	5 / 476 (1.05%)	5 / 475 (1.05%)
occurrences (all)	8	5	5
Malignant hypertension			

subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Peripheral venous disease			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	1	1	0
Phlebitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Varicophlebitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Varicose vein			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hyperpyrexia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Inflammation			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	1 / 475 (0.21%)
occurrences (all)	0	2	1
Oedema peripheral			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Procedural failure			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 474 (0.42%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences (all)	2	3	2
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Atopy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Food allergy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1

Hypersensitivity			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Perennial allergy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Breast disorder			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Breast mass			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Menorrhagia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Menstruation irregular			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Metrorrhagia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Prostatitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	125 / 474 (26.37%)	114 / 476 (23.95%)	125 / 475 (26.32%)
occurrences (all)	189	163	200
Catarrh			

subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	2	1	0
Cough			
subjects affected / exposed	8 / 474 (1.69%)	7 / 476 (1.47%)	9 / 475 (1.89%)
occurrences (all)	9	9	10
Dysphonia			
subjects affected / exposed	4 / 474 (0.84%)	8 / 476 (1.68%)	7 / 475 (1.47%)
occurrences (all)	4	8	7
Dyspnoea			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	2 / 475 (0.42%)
occurrences (all)	1	1	2
Epistaxis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Larynx irritation			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	3	1	1
Nasal obstruction			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Nasal polyps			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Nasal septum deviation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal discomfort			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			

subjects affected / exposed	5 / 474 (1.05%)	8 / 476 (1.68%)	2 / 475 (0.42%)
occurrences (all)	5	8	2
Pleurisy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	2	1	0
Respiratory tract congestion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	8 / 474 (1.69%)	3 / 476 (0.63%)	6 / 475 (1.26%)
occurrences (all)	8	3	6
Rhinorrhoea			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Throat irritation			
subjects affected / exposed	0 / 474 (0.00%)	5 / 476 (1.05%)	1 / 475 (0.21%)
occurrences (all)	0	5	1
Tonsillar hypertrophy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	2
Vasomotor rhinitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Vocal cord inflammation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1

Depression			
subjects affected / exposed	0 / 474 (0.00%)	3 / 476 (0.63%)	0 / 475 (0.00%)
occurrences (all)	0	3	0
Insomnia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	2	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	2	0	1
Blood glucose increased			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Breath sounds abnormal			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Crystal urine			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Haemoglobin increased			

subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Red blood cells urine			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Bronchial injury			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Chest injury			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Contusion			
subjects affected / exposed	4 / 474 (0.84%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	4	0	1
Epicondylitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Exposure to allergen			
subjects affected / exposed	9 / 474 (1.90%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences (all)	9	3	2
Fall			

subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	1 / 475 (0.21%)
occurrences (all)	0	2	1
Fibula fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Joint dislocation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	0 / 474 (0.00%)	3 / 476 (0.63%)	0 / 475 (0.00%)
occurrences (all)	0	3	0
Ligament sprain			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Lip injury			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Medication error			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	2 / 475 (0.42%)
occurrences (all)	0	0	2
Muscle strain			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Skin abrasion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Spinal column injury			

subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Thermal burn			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Upper limb fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Bundle branch block left			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Cardiac failure chronic			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Coronary artery disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	2
Palpitations			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	1 / 474 (0.21%)	2 / 476 (0.42%)	2 / 475 (0.42%)
occurrences (all)	1	2	2
Supraventricular tachycardia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0

Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Convulsions local			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	2 / 475 (0.42%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	10 / 474 (2.11%)	15 / 476 (3.15%)	9 / 475 (1.89%)
occurrences (all)	10	16	10
Hemianopia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Hypersomnia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Intercostal neuralgia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	4 / 475 (0.84%)
occurrences (all)	0	1	4
Muscle contractions involuntary			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Neuritis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			

subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Phantom limb syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Polyneuropathy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	2	0	1
Syncope			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Tension headache			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Haemolysis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Lymphadenitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Tinnitus			

subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Conjunctivitis allergic			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	2 / 475 (0.42%)
occurrences (all)	1	0	2
Eye disorder			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Eye pruritus			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Maculopathy			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Panophthalmitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	1	1	0
Abdominal distension			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Abdominal hernia			

subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	3 / 474 (0.63%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	4	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	2	1	0
Aphthous ulcer			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Chronic gastritis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 474 (0.42%)	5 / 476 (1.05%)	4 / 475 (0.84%)
occurrences (all)	2	5	4
Dry mouth			
subjects affected / exposed	3 / 474 (0.63%)	1 / 476 (0.21%)	5 / 475 (1.05%)
occurrences (all)	3	1	5
Duodenitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	2 / 474 (0.42%)	3 / 476 (0.63%)	1 / 475 (0.21%)
occurrences (all)	2	3	1
Enteritis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Gastritis			

subjects affected / exposed	4 / 474 (0.84%)	4 / 476 (0.84%)	1 / 475 (0.21%)
occurrences (all)	4	4	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 474 (0.21%)	2 / 476 (0.42%)	2 / 475 (0.42%)
occurrences (all)	1	3	2
Haemorrhoids			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Hiatus hernia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Inguinal hernia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hyperchlorhydria			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Large intestine polyp			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Lip dry			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 474 (0.63%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	3	1	0
Pancreatitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Pancreatitis chronic			
subjects affected / exposed	1 / 474 (0.21%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	1	2	0
Salivary gland calculus			

subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Umbilical hernia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	7 / 474 (1.48%)	3 / 476 (0.63%)	4 / 475 (0.84%)
occurrences (all)	7	3	4
Vomiting			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hepatic steatosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Liver disorder			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Dry skin			

subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Psoriasis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Leukocyturia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Nephrolithiasis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Nocturia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Pyelocaliectasis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Renal colic			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1

Urinary incontinence			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	1	1	0
Thyroid cyst			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 474 (0.84%)	5 / 476 (1.05%)	2 / 475 (0.42%)
occurrences (all)	4	5	3
Arthritis			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	5 / 474 (1.05%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences (all)	5	3	2
Bone pain			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Costochondritis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Fibromyalgia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Haemarthrosis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Joint effusion			

subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 474 (0.21%)	2 / 476 (0.42%)	1 / 475 (0.21%)
occurrences (all)	1	2	1
Neck pain			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Osteoarthritis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Osteochondrosis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Osteoporosis postmenopausal			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 474 (0.21%)	3 / 476 (0.63%)	1 / 475 (0.21%)
occurrences (all)	1	3	1
Polyarthritis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Synovial cyst			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Tendonitis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Acute sinusitis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	3 / 475 (0.63%)
occurrences (all)	0	2	4
Bacterial infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Bacterial vaginosis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	21 / 474 (4.43%)	22 / 476 (4.62%)	19 / 475 (4.00%)
occurrences (all)	21	23	24
Candida infection			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	2
Cellulitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Chronic hepatitis C			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Cystitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1

Ear infection fungal			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Erysipelas			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Eye infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 474 (0.21%)	5 / 476 (1.05%)	3 / 475 (0.63%)
occurrences (all)	1	5	3
Gingivitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Infection			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	9 / 474 (1.90%)	5 / 476 (1.05%)	4 / 475 (0.84%)
occurrences (all)	9	5	4
Laryngitis			
subjects affected / exposed	3 / 474 (0.63%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences (all)	3	3	2
Laryngitis viral			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	2	1	0

Localised infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	6 / 474 (1.27%)	6 / 476 (1.26%)	7 / 475 (1.47%)
occurrences (all)	8	7	7
Nasopharyngitis			
subjects affected / exposed	34 / 474 (7.17%)	34 / 476 (7.14%)	43 / 475 (9.05%)
occurrences (all)	36	38	53
Oral candidiasis			
subjects affected / exposed	1 / 474 (0.21%)	2 / 476 (0.42%)	4 / 475 (0.84%)
occurrences (all)	1	3	4
Oral herpes			
subjects affected / exposed	2 / 474 (0.42%)	2 / 476 (0.42%)	1 / 475 (0.21%)
occurrences (all)	2	2	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	2 / 474 (0.42%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	2	0	0
Perichondritis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	18 / 474 (3.80%)	17 / 476 (3.57%)	10 / 475 (2.11%)
occurrences (all)	19	17	10
Pharyngitis bacterial			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	1	0	1
Pharyngotonsillitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Pilonidal cyst			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0

Pneumonia			
subjects affected / exposed	2 / 474 (0.42%)	3 / 476 (0.63%)	2 / 475 (0.42%)
occurrences (all)	2	3	2
Post procedural infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	6 / 474 (1.27%)	2 / 476 (0.42%)	3 / 475 (0.63%)
occurrences (all)	6	2	3
Respiratory tract infection viral			
subjects affected / exposed	10 / 474 (2.11%)	9 / 476 (1.89%)	6 / 475 (1.26%)
occurrences (all)	13	10	6
Rhinitis			
subjects affected / exposed	7 / 474 (1.48%)	5 / 476 (1.05%)	4 / 475 (0.84%)
occurrences (all)	7	5	4
Sinobronchitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	4 / 474 (0.84%)	8 / 476 (1.68%)	9 / 475 (1.89%)
occurrences (all)	4	9	9
Skin infection			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Tinea versicolour			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 474 (0.00%)	3 / 476 (0.63%)	3 / 475 (0.63%)
occurrences (all)	0	3	3
Tonsillitis bacterial			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0

Tooth infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Tracheitis			
subjects affected / exposed	4 / 474 (0.84%)	1 / 476 (0.21%)	6 / 475 (1.26%)
occurrences (all)	4	1	6
Tracheobronchitis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 476 (0.42%)	0 / 475 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	13 / 474 (2.74%)	10 / 476 (2.10%)	9 / 475 (1.89%)
occurrences (all)	14	11	9
Upper respiratory tract infection bacterial			
subjects affected / exposed	5 / 474 (1.05%)	9 / 476 (1.89%)	9 / 475 (1.89%)
occurrences (all)	5	11	11
Urinary tract infection			
subjects affected / exposed	6 / 474 (1.27%)	5 / 476 (1.05%)	4 / 475 (0.84%)
occurrences (all)	6	5	4
Viral infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Viral pharyngitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Viral rhinitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Viral tracheitis			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 474 (1.69%)	11 / 476 (2.31%)	10 / 475 (2.11%)
occurrences (all)	9	11	10
Vulvovaginal candidiasis			

subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	0 / 475 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	1 / 474 (0.21%)	0 / 476 (0.00%)	2 / 475 (0.42%)
occurrences (all)	1	0	2
Dyslipidaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	0	1	1
Gout			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	1	2	1
Hyperglycaemia			
subjects affected / exposed	2 / 474 (0.42%)	1 / 476 (0.21%)	1 / 475 (0.21%)
occurrences (all)	2	1	1
Hyperuricaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Mineral metabolism disorder			
subjects affected / exposed	0 / 474 (0.00%)	0 / 476 (0.00%)	1 / 475 (0.21%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 474 (0.21%)	1 / 476 (0.21%)	0 / 475 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2017	The primary reasons for this amendment were to ensure consistency across sections of the protocol and to update drug supply sourcing strategies and operational details/processes. Protocol sections were harmonized with respect to the escalation and de-escalation of controller or maintenance therapy allowed during the treatment period. The drug supply sourcing strategy was updated as local sourcing for the comparative treatment arm (salmeterol/fluticasone and tiotropium) and the run-in medication (salmeterol/fluticasone) could occur, in addition to global sourcing.
16 November 2017	At the time of randomization, the Investigator needed to make an informed decision about the most appropriate treatment for each individual patient. If the most appropriate treatment was not a LABA+LAMA+ICS, the patient should be screenfailed and be treated according to his/her individual needs. The purpose of this amendment was to support this informed decision-making by adding relevant assessments at the run-in visit, (i.e., measurement of blood total IgE and antigen-specific IgE (ImmunoCAP) for common perennial aeroallergens). Furthermore, this amendment included a change in the hypotheses testing strategy. The key secondary objective (To evaluate efficacy of QVM149 high ICS dose and QVM149 medium ICS dose compared to salmeterol/fluticasone + tiotropium in terms of Trough FEV1 after 24 weeks of treatment) was treated as a regular secondary objective. In addition, the amendment addressed comments received from the Ethics Committee and Health Authority in Germany to clarify some procedures and data protection measures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported