NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Indacaterol acetate/ Glycopyrronium bromide/ Mometasone furoate

Trial Indication(s)

Asthma

Protocol Number

CQVM149B2306

Protocol Title

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

Clinical Trial Phase

Phase 3B

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: February 2018 (Actual)
Primary Completion Date: July 2019 (Actual)
Study Completion Date: July 2019 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This Phase IIIb multicenter study used a randomized, partially-blinded, 24-week, parallel-group, non-inferiority, open-label active controlled design.

The study consisted of a screening period of up to 1-week, run-in period of 2-weeks, randomized treatment period of 24-weeks, and a follow-up period of 1-week. The study used two doses of QVM149 (high dose [150/50/160 µg] and a medium dose [150/50/80 µg] once daily (o.d.) delivered via Concept1 inhaler) and a comparator treatment (salmeterol/fluticasone 50/500 µg twice daily (b.i.d.) delivered via Accuhaler® plus tiotropium 5 µg o.d delivered via Respimat®). Investigators and patients had knowledge of treatment allocation between QVM149 and comparator; however, the QVM149 strength allocation was masked. The global sponsor team responsible for data review and analysis was blinded to all treatment allocations.

At the screening visit, informed consent was obtained, and current and prohibited medications were reviewed. Rescue medication was provided to all patients who met the eligibility criteria and was to be used on an “as needed” basis throughout the study.

At the run-in visit, inclusion and exclusion criteria were reviewed and patients who met the elegibility criteria were supplied with open-label long acting β2-adrenergic agonist/inhaled corticosteroids (LABA/ICS) salmeterol/fluticasone 50/250 µg b.i.d or 50/500 µg b.i.d to match their ICS background medication dose to be stopped at randomization visit.

At randomization visit, patients were randomized to 1 of 3 treatment arms with a randomization ratio of 1:1:1. The planned duration of treatment in this study was 24 weeks and treatment period visits were scheduled every 8 weeks.

All randomized patients were contacted by telephone 7 days following the last dose of study medication or last visit, whichever was later, for the Safety Follow-up visit.

Centers

166 centers in 20 countries: Germany(41), Argentina(29), Turkey(3), Hungary(8), Russia(18), Israel(4), Czech Republic(5), Greece(5), Taiwan(3), South Africa(6), India(9), Vietnam(3), Spain(5), Peru(4), Colombia(3), Poland(4), Slovakia (Slovak Republic)(6), Serbia(5), Mexico(3), Chile(2)

Objectives:

The primary objective 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.

The secondary objectives were to evaluate efficacy of QVM149 high-dose (150/50/160 µg) and QVM149 medium-dose (150/50/80 µg) compared to salmeterol/fluticasone + tiotropium in terms of AQLQ, Asthma Control Questionnaire (ACQ-7), trough Forced Expiratory Volume in the 1st second (FEV1), Forced Vital Capacity (FVC), and Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF25-75).

Test Product (s), Dose(s), and Mode(s) of Administration

- QVM149 (indacaterol acetate/glycopyrronium bromide/mometasone furoate) supplied as powder hard capsules at dose strength of 150/50/80 µg and 150/50/160 µg to be delivered via Concept1 o.d.
- Salmeterol/fluticasone 50/500 µg supplied as dry powder to be delivered via Accuhaler® b.i.d and tiotropium 5 µg supplied as an aqueous solution to be delivered via Respimat® o.d.

Statistical Methods

For the primary objective, the non-inferiority of QVM149 150/50/160 µg o.d. vs.free combination of salmeterol/fluticasone 50/500 µg b.i.d. + tiotropium 5 µg o.d and QVM149 150/50/80 µg o.d. vs. free combination of salmeterol/fluticasone 50/500 µg b.i.d. + tiotropium 5 µg o.d., in terms of change from baseline in AQLQ total score at Week 24, was assessed.

The primary endpoint was analyzed using a mixed model for repeated measurements (MMRM) on the Full Analysis Set (FAS). The model contained treatment, region, visit, background ICS/LABA (medium or high dose), baseline-by-visit interaction and treatment-by-visit interaction as fixed effects with baseline AQLQ total score as the covariate, and center nested within region as a random effect. Since an improvement of 0.5 points in AQLQ score is considered to be the minimal important difference (MCID) in asthma, a non-inferiority margin of one-half of this difference was used. Thus, a non-inferiority margin of 0.25 points reduction in AQLQ score was designated for the study based upon 50% of the MCID. Moreover, to control the family-wise type-I error rate at the one-sided 2.5% significance level, a multiple testing procedure based on the trimmed Simes test was used. The least squares (LS) means of the treatment differences, standard errors, 97.5% (one-sided) confidence interval (CI), and adjusted one-sided p-values for non-inferiority test and nominal two-sided p-values at Week 24 of each QVM149 dose versus the combination of salmeterol/fluticasone 50/500 µg + tiotropium 5 µg, was assessed. Non-inferiority of QVM149 was claimed if the multiplicity adjusted one-sided p-value was < 0.025.

For the key secondary endpoints (ACQ-7 score, trough FEV1, FVC, FEF25-75), the changes from baseline and the between-treatment comparisons were analyzed using the similar MMRM (including all available visits) on the FAS, as used for the primary analysis with respective appropriate baseline. The proportion of patients who achieved the MCID in AQLQ total score ≥ 0.5 increase and ACQ-7 ≥ 0.5 decrease from baseline over the 24 weeks of treatment at post-baseline visits were analyzed using the logistic regression model via the generalized estimate equations.

Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Patients with a diagnosis of asthma for a period of at least 6 months prior to Visit 1 with current asthma severity ≥ step 4 (GINA 2017).
• Patients who had used ICS/LABA combinations for asthma for at least 3 months and at stable medium or high dose of ICS/LABA for at least 1 month prior to Visit 1.
• Patients were required to be symptomatic at screening despite treatment with medium or high stable doses of ICS/LABA as defined by ACQ-7 score ≥ 1.5 at visits 101 and 201 (randomization visit).
• Patients with history of at least one severe asthma exacerbation which required medical care from a physician, emergency room visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1 and required systemic corticosteroid treatment for at least 3 days including physician guided self-management treatment with oral corticosteroids as part of written asthma action plan.
• Pre-bronchodilator FEV1 of < 85 % of the predicted normal value for the patient after withholding bronchodilators prior to spirometry at both Visit 101 and Visit 201.
• Patients who demonstrated an increase in FEV1 of ≥ 12% and 200 ml.

Exclusion Criteria:
• Patients who had a smoking history of greater than 20 pack years.
• Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD).
• Patients who had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening).
• Patients treated with a LAMA for asthma within 3 months prior to Visit 1.
• Patients who had a respiratory tract infection or clinical significant asthma worsening as defined by Investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 201.

Participant Flow Table

Overall Study

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Total
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®	
Started	474	476	476	1426
Full Analysis Set (FAS)	474	476	475	1425
Safety Set (SAF)	474	476	475	1425
Completed	452	460	448	1360
Not Completed	22	16	28	66
Subject/Guardian Decision	10	6	11	27
Adverse Event	5	3	3	11

Techinical Problems	3	1	5	9
Physician Decision	2	3	7	12
Lost to Follow-up	1	1	1	3
Sponsor decision	1	0	0	1
Pregnancy	0	2	0	2
Randomized in error	0	0	1	1

Baseline Characteristics

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Total
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®	
Number of Participants [units: participants]	474	476	476	1426
Age Continuous (units: Years) Mean ± Standard Deviation				
	51.9±13.58	52.7±13.34	53.1±13.08	52.5±13.33
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				

Female	306	289	307	902
Male	168	187	169	524
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)				
American Indian or Alaska Native	5	1	10	16
Asian	36	34	33	103
Black or African American	6	5	3	14
White	401	392	391	1184
Other	26	44	39	109

Summary of Efficacy

Primary Outcome Result(s)

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

(Time Frame: Baseline and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®

Number of Participants Analyzed [units: participants]	436	453	435
Change from Baseline in Asthma Quality of Life Questionnaire (AQLQ) Total Score (units: Score on a scale) Least Squares Mean ± Standard Error			
	0.715 ± 0.070	0.827 ± 0.069	0.753 ± 0.069

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
Non-Inferiority/Equivalence Test	Non-Inferiority	Non-inferiority margin: 0.25 points
P Value	<0.001	P-Value is one-sided
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other Least Square mean (LS Mean)	-0.038	
Standard Error of the mean	0.051	
97.5 % Confidence Interval 1-Sided	-0.139 to	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone

	50/500 µg plus tiotropium 5 µg	
Non-Inferiority/Equivalence Test	Non-Inferiority	Non-inferiority margin: 0.25 points
P Value	<0.001	P-Value is one-sided
Method	Other MMRM	
Other LS Mean	0.073	
Standard Error of the mean	0.051	
97.5 % Confidence Interval 1-Sided	-0.027 to	

Secondary Outcome Result(s)

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

(Time Frame: Baseline, Week 8, Week 16 and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	420	438	425

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

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.892	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.003	
Standard Error of the mean	0.025	
95 % Confidence Interval 2-Sided	-0.046 to 0.052	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.007	P-value is two-sided
Method	Other MMRM	

Other LS Mean	0.067
Standard Error of the mean	0.025
95 % Confidence Interval 2-Sided	0.018 to 0.115

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.945	P-value is two-sided
Method	Other MMRM	
Other LS Mean	-0.002	
Standard Error of the mean	0.025	
95 % Confidence Interval 2-Sided	-0.050 to 0.047	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.007	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.066	

Standard Error of the mean	0.025
95 % Confidence Interval 2-Sided	0.018 to 0.114

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	0.713	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.009	
Standard Error of the mean	0.026	
95 % Confidence Interval 2-Sided	-0.041 to 0.060	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	<0.001	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.096	
Standard Error of the mean	0.026	

95 % Confidence Interval 2-Sided	0.046 to 0.146

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

(Time Frame: Baseline, Week 16 and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	447	454	447
Change from Baseline in Asthma Control Questionnaire (ACQ-7) Total Score (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 Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.308	P-value is one-sided
Method	Other MMRM	

Other LS Mean	-0.023
Standard Error of the mean	0.046
95 % Confidence Interval 2-Sided	-0.113 to 0.067

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.044	P-value is one-sided
Method	Other MMRM	
Other LS Mean	-0.079	
Standard Error of the mean	0.046	
95 % Confidence Interval 2-Sided	-0.169 to 0.012	

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	0.245	P-value is one sided
Method	Other MMRM	
Other LS Mean	-0.032	

Standard Error of the mean	0.047
95 % Confidence Interval 2-Sided	-0.125 to 0.060

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	0.004	P-value is one sided
Method	Other MMRM	
Other LS Mean	-0.124	
Standard Error of the mean	0.047	
95 % Confidence Interval 2-Sided	-0.216 to -0.032	

Change from Baseline in AQLQ Total Score

(Time Frame: Baseline and Week 16)

	QVM149 150/50/80 µg	**QVM149 150/50/160 µg**	**Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg**
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®

Number of Participants Analyzed [units: participants]	435	442	429
Change from Baseline in AQLQ Total Score (units: Score on a scale) Least Squares Mean ± Standard Error			
	0.690 ± 0.069	0.755 ± 0.068	0.673 ± 0.069

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.719	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.018	
Standard Error of the mean	0.049	
95 % Confidence Interval 2-Sided	-0.079 to 0.115	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.097	P-value is two-sided
Method	Other MMRM	

Other LS Mean	0.082
Standard Error of the mean	0.049
95 % Confidence Interval 2-Sided	-0.015 to 0.179

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

(Time Frame: Baseline and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	447	454	447
Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Decrease from Baseline ACQ-7 ≥ 0.5 (units: Percentage of participants)			
	87.9	85.2	83.9

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.061	P-value is one sided
Method	Regression, Logistic	Logistic Regression Model via Generalized estimating equations (GEE)
Odds Ratio (OR)	1.23	
95 % Confidence Interval 2-Sided	0.94 to 1.61	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.227	P-value is one-sided
Method	Regression, Logistic	Logistic Regression Model via GEE
Odds Ratio (OR)	1.11	
95 % Confidence Interval 2-Sided	0.85 to 1.46	

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

(Time Frame: Baseline and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg
Arm/Group Description	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg b.i.d.

	o.d. delivered via Concept1	o.d. delivered via Concept1	delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	444	454	441
Percentage of Patients Achieving the Minimally Clinically Important Difference (MCID) Change from Baseline AQLQ ≥ 0.5 (units: Percentage of participants)			
	71.6	73.3	67.8

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.108	P-value is one sided
Method	Regression, Logistic	Logistic regression model via the GEE
Odds Ratio (OR)	1.17	
95 % Confidence Interval 2-Sided	0.91 to 1.49	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	
P Value	0.013	P-Value is one sided
Method	Regression, Logistic	Logistic regression model via the GEE
Odds Ratio (OR)	1.33	
95 % Confidence Interval 2-Sided	1.03 to 1.70	

Change from Baseline in Forced Vital Capacity (FVC)

(Time Frame: Baseline, Week 8, Week 16 and Week 24)

	QVM149 150/50/80 µg	**QVM149 150/50/160 µg**	**Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg**
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	420	438	425
Change from Baseline in Forced Vital Capacity (FVC) (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 Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.908	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	-0.003	
Standard Error of the mean	0.027	
95 % Confidence Interval 2-Sided	-0.055 to 0.049	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.046	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.053	
Standard Error of the mean	0.026	
95 % Confidence Interval 2-Sided	0.001 to 0.104	

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.870	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.004	
Standard Error of the mean	0.026	
95 % Confidence Interval 2-Sided	-0.047 to 0.056	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.028	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.058	
Standard Error of the mean	0.026	
95 % Confidence Interval 2-Sided	0.006 to 0.109	

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone	Week 24

	50/500 µg plus tiotropium 5 µg	
P Value	0.303	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.028	
Standard Error of the mean	0.028	
95 % Confidence Interval 2-Sided	-0.026 to 0.083	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	<0.001	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.095	
Standard Error of the mean	0.027	
95 % Confidence Interval 2-Sided	0.041 to 0.148	

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

(Time Frame: Baseline, Week 8, Week 16 and Week 24)

	QVM149 150/50/80 µg	QVM149 150/50/160 µg	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg

Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Number of Participants Analyzed [units: participants]	420	438	425
Change from Baseline in Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF25-75) (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 Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.563	P-value is two-sided
Method	Other MMRM	
Other LS Mean	0.020	
Standard Error of the mean	0.034	

95 % Confidence Interval 2-Sided	-0.048 to 0.087

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 8
P Value	0.068	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.062	
Standard Error of the mean	0.034	
95 % Confidence Interval 2-Sided	-0.005 to 0.129	

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.844	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	-0.007	
Standard Error of the mean	0.035	
95 % Confidence Interval 2-Sided	-0.076 to 0.062	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 16
P Value	0.097	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.058	
Standard Error of the mean	0.035	
95 % Confidence Interval 2-Sided	-0.010 to 0.125	

Statistical Analysis

Groups	QVM149 150/50/80 µg, Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg	Week 24
P Value	0.927	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.003	
Standard Error of the mean	0.036	
95 % Confidence Interval 2-Sided	-0.067 to 0.074	

Statistical Analysis

Groups	QVM149 150/50/160 µg, Salmeterol/fluticasone	Week 24

	50/500 µg plus tiotropium 5 µg	
P Value	0.013	P-Value is two-sided
Method	Other MMRM	
Other LS Mean	0.089	
Standard Error of the mean	0.036	
95 % Confidence Interval 2-Sided	0.019 to 0.159	

Summary of Safety

Safety Results

All-Cause Mortality

	QVM149 150/50/80 µg N = 474	QVM149 150/50/160 µg N = 476	Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg N = 475
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Total participants affected	0 (0.00%)	0 (0.00%)	1 (0.21%)

Serious Adverse Events by System Organ Class

Time Frame	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.
Additional Description	Any sign or symptom that occurs during the study treatment but not later than 7 days (30 days in case of a Serious Adverse Events) after the last administration.
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment

	QVM149 150/50/80 µg N = 474	**QVM149 150/50/160 µg N = 476**	**Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg N = 475**
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Total participants affected	14 (2.95%)	18 (3.78%)	19 (4.00%)
Blood and lymphatic system disorders			
Lymphadenopathy	0 (0.00%)	1 (0.21%)	0 (0.00%)
Cardiac disorders			
Atrioventricular block second degree	1 (0.21%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	0 (0.00%)	1 (0.21%)

Supraventricular tachycardia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Endocrine disorders			
Goitre	0 (0.00%)	1 (0.21%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal hernia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	1 (0.21%)
Colitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Gastrointestinal haemorrhage	1 (0.21%)	0 (0.00%)	0 (0.00%)
Large intestine polyp	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pancreatitis acute	0 (0.00%)	0 (0.00%)	1 (0.21%)
General disorders and administration site conditions			
Hyperpyrexia	1 (0.21%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hepatobiliary disorders			
Cholecystitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Cholecystitis acute	0 (0.00%)	0 (0.00%)	1 (0.21%)
Cholelithiasis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Infections and infestations			
Atypical pneumonia	1 (0.21%)	0 (0.00%)	0 (0.00%)
Bronchiolitis	0 (0.00%)	1 (0.21%)	0 (0.00%)

Cellulitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Diverticulitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
H1N1 influenza	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hepatitis viral	1 (0.21%)	0 (0.00%)	0 (0.00%)
Lung infection	1 (0.21%)	0 (0.00%)	0 (0.00%)
Pilonidal cyst	0 (0.00%)	1 (0.21%)	0 (0.00%)
Pneumonia	0 (0.00%)	5 (1.05%)	0 (0.00%)
Postoperative abscess	1 (0.21%)	0 (0.00%)	0 (0.00%)
Rectal abscess	0 (0.00%)	0 (0.00%)	1 (0.21%)
Viral upper respiratory tract infection	1 (0.21%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Contusion	0 (0.00%)	1 (0.21%)	0 (0.00%)
Intentional product misuse	0 (0.00%)	0 (0.00%)	2 (0.42%)
Meniscus injury	1 (0.21%)	0 (0.00%)	0 (0.00%)
Wrist fracture	0 (0.00%)	0 (0.00%)	1 (0.21%)
Investigations			
Hepatic enzyme increased	1 (0.21%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm	0 (0.00%)	1 (0.21%)	0 (0.00%)
Fibroadenoma of breast	1 (0.21%)	0 (0.00%)	0 (0.00%)

Large intestine benign neoplasm	0 (0.00%)	0 (0.00%)	1 (0.21%)
Respiratory tract neoplasm	0 (0.00%)	1 (0.21%)	0 (0.00%)
Nervous system disorders			
Carotid artery stenosis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Guillain-Barre syndrome	0 (0.00%)	0 (0.00%)	1 (0.21%)
Haemorrhagic stroke	0 (0.00%)	0 (0.00%)	1 (0.21%)
Polyneuropathy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Syncope	1 (0.21%)	0 (0.00%)	0 (0.00%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	0 (0.00%)	1 (0.21%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	1 (0.21%)	0 (0.00%)	0 (0.00%)
Asthma	4 (0.84%)	3 (0.63%)	2 (0.42%)
Bronchiectasis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hypoxia	1 (0.21%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Deep vein thrombosis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Thrombophlebitis superficial	0 (0.00%)	1 (0.21%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	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.
Additional Description	Any sign or symptom that occurs during the study treatment but not later than 7 days (30 days in case of a Serious Adverse Events) after the last administration.
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	QVM149 150/50/80 µg N = 474	**QVM149 150/50/160 µg N = 476**	**Salmeterol/fluticasone 50/500 µg plus tiotropium 5 µg N = 475**
Arm/Group Description	QVM149 150/50/80 µg o.d. delivered via Concept1	QVM149 150/50/160 µg o.d. delivered via Concept1	Salmeterol/fluticasone 50/500 µg b.i.d. delivered via Accuhaler® plus tiotropium 5 µg o.d. delivered via Respimat®
Total participants affected	245 (51.69%)	246 (51.68%)	241 (50.74%)
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	2 (0.42%)	0 (0.00%)
Haemolysis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Lymphadenitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Cardiac disorders			
Angina pectoris	0 (0.00%)	1 (0.21%)	0 (0.00%)
Atrioventricular block first degree	0 (0.00%)	1 (0.21%)	0 (0.00%)
Bundle branch block left	0 (0.00%)	0 (0.00%)	1 (0.21%)

Cardiac failure	0 (0.00%)	1 (0.21%)	0 (0.00%)
Cardiac failure chronic	0 (0.00%)	0 (0.00%)	1 (0.21%)
Coronary artery disease	0 (0.00%)	1 (0.21%)	1 (0.21%)
Palpitations	0 (0.00%)	2 (0.42%)	0 (0.00%)
Sinus tachycardia	1 (0.21%)	2 (0.42%)	2 (0.42%)
Supraventricular tachycardia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Ear and labyrinth disorders			
Deafness	0 (0.00%)	0 (0.00%)	1 (0.21%)
Tinnitus	0 (0.00%)	0 (0.00%)	1 (0.21%)
Endocrine disorders			
Hypothyroidism	1 (0.21%)	1 (0.21%)	0 (0.00%)
Thyroid cyst	0 (0.00%)	1 (0.21%)	0 (0.00%)
Eye disorders			
Blepharitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Cataract	1 (0.21%)	0 (0.00%)	1 (0.21%)
Conjunctivitis allergic	1 (0.21%)	0 (0.00%)	2 (0.42%)
Eye disorder	1 (0.21%)	0 (0.00%)	0 (0.00%)
Eye pruritus	1 (0.21%)	0 (0.00%)	0 (0.00%)
Maculopathy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Panophthalmitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Vision blurred	0 (0.00%)	0 (0.00%)	1 (0.21%)
Gastrointestinal disorders			
Abdominal discomfort	1 (0.21%)	1 (0.21%)	0 (0.00%)

Abdominal distension	0 (0.00%)	1 (0.21%)	0 (0.00%)
Abdominal hernia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Abdominal pain	3 (0.63%)	2 (0.42%)	0 (0.00%)
Abdominal pain upper	2 (0.42%)	1 (0.21%)	0 (0.00%)
Aphthous ulcer	0 (0.00%)	1 (0.21%)	1 (0.21%)
Chronic gastritis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Colitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Constipation	0 (0.00%)	0 (0.00%)	1 (0.21%)
Diarrhoea	2 (0.42%)	5 (1.05%)	4 (0.84%)
Dry mouth	3 (0.63%)	1 (0.21%)	5 (1.05%)
Duodenitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Dyspepsia	2 (0.42%)	3 (0.63%)	1 (0.21%)
Enteritis	1 (0.21%)	0 (0.00%)	1 (0.21%)
Gastritis	4 (0.84%)	4 (0.84%)	1 (0.21%)
Gastrooesophageal reflux disease	1 (0.21%)	2 (0.42%)	2 (0.42%)
Haemorrhoids	1 (0.21%)	0 (0.00%)	0 (0.00%)
Hiatus hernia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hyperchlorhydria	0 (0.00%)	0 (0.00%)	1 (0.21%)
Inguinal hernia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Large intestine polyp	0 (0.00%)	0 (0.00%)	1 (0.21%)
Lip dry	0 (0.00%)	1 (0.21%)	0 (0.00%)
Nausea	3 (0.63%)	1 (0.21%)	0 (0.00%)
Oesophagitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Pancreatitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Pancreatitis chronic	1 (0.21%)	2 (0.42%)	0 (0.00%)

Salivary gland calculus	1 (0.21%)	0 (0.00%)	0 (0.00%)
Toothache	7 (1.48%)	3 (0.63%)	4 (0.84%)
Umbilical hernia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Vomiting	1 (0.21%)	1 (0.21%)	1 (0.21%)
General disorders and administration site conditions			
Asthenia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Chest discomfort	0 (0.00%)	1 (0.21%)	0 (0.00%)
Chest pain	1 (0.21%)	1 (0.21%)	1 (0.21%)
Chills	1 (0.21%)	0 (0.00%)	0 (0.00%)
Discomfort	0 (0.00%)	1 (0.21%)	0 (0.00%)
Fatigue	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hyperpyrexia	1 (0.21%)	0 (0.00%)	0 (0.00%)
Impaired healing	0 (0.00%)	1 (0.21%)	0 (0.00%)
Inflammation	0 (0.00%)	0 (0.00%)	1 (0.21%)
Non-cardiac chest pain	0 (0.00%)	2 (0.42%)	1 (0.21%)
Oedema peripheral	0 (0.00%)	1 (0.21%)	1 (0.21%)
Pain	0 (0.00%)	1 (0.21%)	0 (0.00%)
Procedural failure	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pyrexia	2 (0.42%)	3 (0.63%)	2 (0.42%)
Hepatobiliary disorders			
Cholecystitis chronic	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hepatic steatosis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Liver disorder	0 (0.00%)	0 (0.00%)	1 (0.21%)
Immune system disorders			

Allergy to arthropod bite	0 (0.00%)	0 (0.00%)	1 (0.21%)
Atopy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Food allergy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Hypersensitivity	1 (0.21%)	0 (0.00%)	1 (0.21%)
Perennial allergy	0 (0.00%)	1 (0.21%)	0 (0.00%)
Infections and infestations			
Abscess limb	2 (0.42%)	0 (0.00%)	0 (0.00%)
Acute sinusitis	0 (0.00%)	2 (0.42%)	3 (0.63%)
Bacterial infection	0 (0.00%)	1 (0.21%)	0 (0.00%)
Bacterial vaginosis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Bronchitis	21 (4.43%)	22 (4.62%)	19 (4.00%)
Candida infection	0 (0.00%)	0 (0.00%)	1 (0.21%)
Cellulitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Chronic hepatitis C	0 (0.00%)	1 (0.21%)	0 (0.00%)
Conjunctivitis	2 (0.42%)	0 (0.00%)	0 (0.00%)
Cystitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Ear infection	0 (0.00%)	0 (0.00%)	1 (0.21%)
Ear infection fungal	0 (0.00%)	0 (0.00%)	1 (0.21%)
Erysipelas	2 (0.42%)	0 (0.00%)	0 (0.00%)
Eye infection	0 (0.00%)	1 (0.21%)	0 (0.00%)
Folliculitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	1 (0.21%)	5 (1.05%)	3 (0.63%)
Gingivitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Helicobacter infection	1 (0.21%)	0 (0.00%)	0 (0.00%)
Hordeolum	1 (0.21%)	1 (0.21%)	1 (0.21%)

Infection	0 (0.00%)	0 (0.00%)	1 (0.21%)
Influenza	9 (1.90%)	5 (1.05%)	4 (0.84%)
Laryngitis	3 (0.63%)	3 (0.63%)	2 (0.42%)
Laryngitis viral	1 (0.21%)	1 (0.21%)	0 (0.00%)
Localised infection	1 (0.21%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection	6 (1.27%)	6 (1.26%)	7 (1.47%)
Nasopharyngitis	34 (7.17%)	34 (7.14%)	43 (9.05%)
Oral candidiasis	1 (0.21%)	2 (0.42%)	4 (0.84%)
Oral herpes	2 (0.42%)	2 (0.42%)	1 (0.21%)
Oropharyngeal candidiasis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Otitis media	2 (0.42%)	0 (0.00%)	0 (0.00%)
Perichondritis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pharyngitis	18 (3.80%)	17 (3.57%)	10 (2.11%)
Pharyngitis bacterial	1 (0.21%)	0 (0.00%)	1 (0.21%)
Pharyngotonsillitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Pilonidal cyst	0 (0.00%)	1 (0.21%)	0 (0.00%)
Pneumonia	2 (0.42%)	3 (0.63%)	2 (0.42%)
Post procedural infection	0 (0.00%)	1 (0.21%)	0 (0.00%)
Pulpitis dental	0 (0.00%)	0 (0.00%)	1 (0.21%)
Respiratory tract infection	6 (1.27%)	2 (0.42%)	3 (0.63%)
Respiratory tract infection viral	10 (2.11%)	9 (1.89%)	6 (1.26%)
Rhinitis	7 (1.48%)	5 (1.05%)	4 (0.84%)
Sinobronchitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Sinusitis	4 (0.84%)	8 (1.68%)	9 (1.89%)

Skin infection	0 (0.00%)	0 (0.00%)	1 (0.21%)
Tinea versicolour	0 (0.00%)	1 (0.21%)	0 (0.00%)
Tonsillitis	0 (0.00%)	3 (0.63%)	3 (0.63%)
Tonsillitis bacterial	1 (0.21%)	0 (0.00%)	0 (0.00%)
Tooth infection	1 (0.21%)	1 (0.21%)	1 (0.21%)
Tracheitis	4 (0.84%)	1 (0.21%)	6 (1.26%)
Tracheobronchitis	0 (0.00%)	2 (0.42%)	0 (0.00%)
Upper respiratory tract infection	13 (2.74%)	10 (2.10%)	9 (1.89%)
Upper respiratory tract infection bacterial	5 (1.05%)	9 (1.89%)	9 (1.89%)
Urinary tract infection	6 (1.27%)	5 (1.05%)	4 (0.84%)
Viral infection	1 (0.21%)	1 (0.21%)	1 (0.21%)
Viral pharyngitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Viral rhinitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Viral tracheitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Viral upper respiratory tract infection	8 (1.69%)	11 (2.31%)	10 (2.11%)
Vulvovaginal candidiasis	1 (0.21%)	1 (0.21%)	1 (0.21%)
Injury, poisoning and procedural complications			
Animal bite	1 (0.21%)	0 (0.00%)	0 (0.00%)
Bronchial injury	0 (0.00%)	0 (0.00%)	1 (0.21%)
Chest injury	1 (0.21%)	1 (0.21%)	1 (0.21%)
Contusion	4 (0.84%)	0 (0.00%)	1 (0.21%)
Epicondylitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Exposure to allergen	9 (1.90%)	3 (0.63%)	2 (0.42%)

Fall	0 (0.00%)	2 (0.42%)	1 (0.21%)
Fibula fracture	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hand fracture	0 (0.00%)	0 (0.00%)	1 (0.21%)
Joint dislocation	1 (0.21%)	0 (0.00%)	0 (0.00%)
Joint injury	0 (0.00%)	3 (0.63%)	0 (0.00%)
Ligament sprain	1 (0.21%)	0 (0.00%)	1 (0.21%)
Lip injury	0 (0.00%)	1 (0.21%)	0 (0.00%)
Medication error	0 (0.00%)	0 (0.00%)	2 (0.42%)
Muscle strain	0 (0.00%)	0 (0.00%)	1 (0.21%)
Radius fracture	0 (0.00%)	0 (0.00%)	1 (0.21%)
Rib fracture	0 (0.00%)	2 (0.42%)	0 (0.00%)
Skin abrasion	1 (0.21%)	0 (0.00%)	0 (0.00%)
Spinal column injury	2 (0.42%)	0 (0.00%)	0 (0.00%)
Thermal burn	0 (0.00%)	1 (0.21%)	0 (0.00%)
Upper limb fracture	1 (0.21%)	0 (0.00%)	0 (0.00%)
Investigations			
Alanine aminotransferase increased	1 (0.21%)	0 (0.00%)	1 (0.21%)
Aspartate aminotransferase increased	2 (0.42%)	1 (0.21%)	1 (0.21%)
Blood alkaline phosphatase increased	2 (0.42%)	0 (0.00%)	1 (0.21%)
Blood glucose increased	0 (0.00%)	0 (0.00%)	1 (0.21%)
Blood uric acid increased	0 (0.00%)	0 (0.00%)	1 (0.21%)
Breath sounds abnormal	0 (0.00%)	0 (0.00%)	1 (0.21%)

Crystal urine	0 (0.00%)	0 (0.00%)	1 (0.21%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	1 (0.21%)
Haemoglobin increased	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hepatic enzyme increased	0 (0.00%)	0 (0.00%)	1 (0.21%)
Liver function test increased	1 (0.21%)	0 (0.00%)	0 (0.00%)
Red blood cells urine	0 (0.00%)	0 (0.00%)	1 (0.21%)
Weight decreased	0 (0.00%)	1 (0.21%)	0 (0.00%)
Metabolism and nutrition disorders			
Decreased appetite	1 (0.21%)	0 (0.00%)	0 (0.00%)
Dehydration	0 (0.00%)	0 (0.00%)	1 (0.21%)
Diabetes mellitus	1 (0.21%)	0 (0.00%)	2 (0.42%)
Dyslipidaemia	0 (0.00%)	1 (0.21%)	1 (0.21%)
Gout	1 (0.21%)	1 (0.21%)	1 (0.21%)
Hyperglycaemia	2 (0.42%)	1 (0.21%)	1 (0.21%)
Hyperuricaemia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hypoglycaemia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Mineral metabolism disorder	0 (0.00%)	0 (0.00%)	1 (0.21%)
Type 2 diabetes mellitus	1 (0.21%)	1 (0.21%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	4 (0.84%)	5 (1.05%)	2 (0.42%)
Arthritis	1 (0.21%)	1 (0.21%)	0 (0.00%)

Back pain	5 (1.05%)	3 (0.63%)	2 (0.42%)
Bone pain	1 (0.21%)	0 (0.00%)	0 (0.00%)
Costochondritis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Fibromyalgia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Haemarthrosis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Intervertebral disc protrusion	0 (0.00%)	0 (0.00%)	1 (0.21%)
Joint effusion	0 (0.00%)	1 (0.21%)	1 (0.21%)
Muscle spasms	1 (0.21%)	0 (0.00%)	1 (0.21%)
Musculoskeletal pain	1 (0.21%)	2 (0.42%)	1 (0.21%)
Neck pain	1 (0.21%)	1 (0.21%)	1 (0.21%)
Osteoarthritis	1 (0.21%)	0 (0.00%)	1 (0.21%)
Osteochondrosis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Osteoporosis postmenopausal	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pain in extremity	1 (0.21%)	3 (0.63%)	1 (0.21%)
Polyarthritis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Rotator cuff syndrome	1 (0.21%)	0 (0.00%)	0 (0.00%)
Spinal pain	0 (0.00%)	0 (0.00%)	1 (0.21%)
Synovial cyst	1 (0.21%)	0 (0.00%)	0 (0.00%)
Tendonitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm	0 (0.00%)	0 (0.00%)	1 (0.21%)
Prostatic adenoma	0 (0.00%)	1 (0.21%)	0 (0.00%)

Respiratory tract neoplasm	0 (0.00%)	1 (0.21%)	0 (0.00%)
Uterine leiomyoma	0 (0.00%)	0 (0.00%)	1 (0.21%)
Nervous system disorders			
Burning sensation	0 (0.00%)	1 (0.21%)	1 (0.21%)
Convulsions local	0 (0.00%)	0 (0.00%)	1 (0.21%)
Dizziness	1 (0.21%)	0 (0.00%)	2 (0.42%)
Headache	10 (2.11%)	15 (3.15%)	9 (1.89%)
Hemianopia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Hypersomnia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Intercostal neuralgia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Migraine	0 (0.00%)	1 (0.21%)	4 (0.84%)
Muscle contractions involuntary	0 (0.00%)	1 (0.21%)	0 (0.00%)
Neuritis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Paraesthesia	0 (0.00%)	2 (0.42%)	0 (0.00%)
Phantom limb syndrome	1 (0.21%)	0 (0.00%)	0 (0.00%)
Polyneuropathy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Presyncope	0 (0.00%)	1 (0.21%)	0 (0.00%)
Sciatica	2 (0.42%)	0 (0.00%)	1 (0.21%)
Syncope	0 (0.00%)	0 (0.00%)	1 (0.21%)
Tension headache	1 (0.21%)	0 (0.00%)	1 (0.21%)
Psychiatric disorders			
Anxiety	0 (0.00%)	0 (0.00%)	1 (0.21%)
Depression	0 (0.00%)	3 (0.63%)	0 (0.00%)

Insomnia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Restlessness	0 (0.00%)	0 (0.00%)	1 (0.21%)
Renal and urinary disorders			
Chronic kidney disease	0 (0.00%)	1 (0.21%)	0 (0.00%)
Leukocyturia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Nephrolithiasis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Nocturia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Pyelocaliectasis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Renal colic	0 (0.00%)	0 (0.00%)	1 (0.21%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	1 (0.21%)
Reproductive system and breast disorders			
Breast cyst	0 (0.00%)	0 (0.00%)	1 (0.21%)
Breast disorder	0 (0.00%)	0 (0.00%)	1 (0.21%)
Breast mass	1 (0.21%)	0 (0.00%)	0 (0.00%)
Menorrhagia	0 (0.00%)	0 (0.00%)	1 (0.21%)
Menstruation irregular	0 (0.00%)	0 (0.00%)	1 (0.21%)
Metrorrhagia	0 (0.00%)	1 (0.21%)	0 (0.00%)
Prostatitis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Asthma	125 (26.37%)	114 (23.95%)	125 (26.32%)
Catarrh	2 (0.42%)	1 (0.21%)	0 (0.00%)
Cough	8 (1.69%)	7 (1.47%)	9 (1.89%)
Dysphonia	4 (0.84%)	8 (1.68%)	7 (1.47%)

Dyspnoea	1 (0.21%)	1 (0.21%)	2 (0.42%)
Epistaxis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Haemoptysis	0 (0.00%)	1 (0.21%)	1 (0.21%)
Larynx irritation	0 (0.00%)	0 (0.00%)	1 (0.21%)
Nasal congestion	2 (0.42%)	1 (0.21%)	1 (0.21%)
Nasal obstruction	1 (0.21%)	0 (0.00%)	0 (0.00%)
Nasal polyps	0 (0.00%)	0 (0.00%)	1 (0.21%)
Nasal septum deviation	0 (0.00%)	1 (0.21%)	0 (0.00%)
Oropharyngeal discomfort	1 (0.21%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	5 (1.05%)	8 (1.68%)	2 (0.42%)
Pleurisy	0 (0.00%)	1 (0.21%)	0 (0.00%)
Productive cough	2 (0.42%)	1 (0.21%)	0 (0.00%)
Respiratory tract congestion	1 (0.21%)	0 (0.00%)	0 (0.00%)
Rhinitis allergic	8 (1.69%)	3 (0.63%)	6 (1.26%)
Rhinorrhoea	1 (0.21%)	0 (0.00%)	0 (0.00%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	1 (0.21%)
Throat irritation	0 (0.00%)	5 (1.05%)	1 (0.21%)
Tonsillar hypertrophy	0 (0.00%)	0 (0.00%)	1 (0.21%)
Vasomotor rhinitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Vocal cord inflammation	0 (0.00%)	1 (0.21%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Alopecia	1 (0.21%)	0 (0.00%)	0 (0.00%)
Dermatitis allergic	0 (0.00%)	1 (0.21%)	0 (0.00%)
Dermatitis atopic	0 (0.00%)	0 (0.00%)	1 (0.21%)

Dermatitis contact	0 (0.00%)	0 (0.00%)	1 (0.21%)
Dry skin	0 (0.00%)	0 (0.00%)	1 (0.21%)
Eczema	0 (0.00%)	1 (0.21%)	1 (0.21%)
Pruritus	2 (0.42%)	0 (0.00%)	0 (0.00%)
Psoriasis	0 (0.00%)	1 (0.21%)	0 (0.00%)
Skin burning sensation	1 (0.21%)	0 (0.00%)	0 (0.00%)
Urticaria	1 (0.21%)	0 (0.00%)	1 (0.21%)
Surgical and medical procedures			
Tooth extraction	0 (0.00%)	1 (0.21%)	0 (0.00%)
Vascular disorders			
Hot flush	0 (0.00%)	0 (0.00%)	1 (0.21%)
Hypertension	7 (1.48%)	5 (1.05%)	5 (1.05%)
Malignant hypertension	1 (0.21%)	0 (0.00%)	0 (0.00%)
Peripheral venous disease	1 (0.21%)	1 (0.21%)	0 (0.00%)
Phlebitis	0 (0.00%)	0 (0.00%)	1 (0.21%)
Varicophlebitis	1 (0.21%)	0 (0.00%)	0 (0.00%)
Varicose vein	1 (0.21%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

Both high (150/50/160 µg) and medium (150/50/80 µg) QVM149 doses demonstrated non-inferiority with respect to the change from baseline in AQLQ after 24 weeks of treatment compared to the standard of care treatment consisting of a high dose of salmeterol/fluticasone + tiotropium.

In general, the high QVM149 dose showed consistent improvements in the efficacy endpoints in patients with uncontrolled asthma compared to salmeterol/fluticasone + tiotropium over 24 weeks such as the proportion of patients who achieved MCID in AQLQ and ACQ-7 scores and lung function parameters (trough FEV1, FVC and FEF25-75), while the medium QVM149 dose showed comparable efficacy to the high dose salmeterol/fluticasone + tiotropium.

Overall safety was comparable across the treatment arms. Both high and medium doses of QVM149 have shown a comparable safety profile to the high dose of salmeterol/fluticasone + tiotropium, which is a commercially available combination for standard of care in asthma, with a well-established safety profile.

Date of Clinical Trial Report

25-Feb-2020