Clinical trial results:
A randomized, double-blind, double-dummy, activecontrolled,3-period complete cross-over study to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone in patients with asthma.

Summary

EudraCT number	2016-005164-34
Trial protocol	NL GB BG RO
Global end of trial date	02 August 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	CQVM149B2208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03063086
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61324111, 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	02 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg once daily (o.d.) compared to a fixed-dose combination (FDC) of salmeterol/fluticasone at a dose of 50/500 µg twice daily (b.i.d.) after 3 weeks of treatment in patients with asthma.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2017
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	Bulgaria: 25
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Romania: 9
Worldwide total number of subjects	116
EEA total number of subjects	108

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)	98
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

114 patients were planned to be randomized to one of the six treatment sequences in an equal allocation ratio. Procedures in all treatment periods
were identical. At the end of the last treatment period, the patients underwent Study Completion evaluations before they were discharged from the study site

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1 (A-B-C)

Arm description:

QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.

Arm type	Active comparator
Investigational medicinal product name	QVM149 150/50/80 µg o.d.; QVM149 150/50/160 µg o.d.; salmeterol/fluticasone FDC 50/500 µg b.i.d.
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

oral inhalation

Arm title	Sequence 2(A-C-B)

Arm description:

QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d;

Arm type	Active comparator
Investigational medicinal product name	QVM149 150/50/80 µg o.d.; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d.;
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

oral inhalation

Arm title	Sequence 3(B-C-A)

Arm description:

QVM149 150/50/160 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/80 µg o.d

Arm type	Active comparator

Investigational medicinal product name	QVM149 150/50/160 µg o.d.; salmeterol/fluticasone FDC 50/500 µg b.i.d; QVM149 150/50/80 µg o.d.;
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Oral inhalation

Arm title	Sequence 4(B-A-C)

Arm description:

QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d

Arm type	Active comparator
Investigational medicinal product name	QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Oral Inhalation

Arm title	Sequence 5(C-A-B)

Arm description:

salmeterol/fluticasone FDC 50/500 µg b.i.d; QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d

Arm type	Active comparator
Investigational medicinal product name	salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d.;
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Oral Inhalation

Arm title	Sequence 6(C-B-A)

Arm description:

salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d

Arm type	Active comparator
Investigational medicinal product name	salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d.; QVM149 150/50/80 µg o.d
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Oral Inhalation

Number of subjects in period 1	Sequence 1 (A-B-C)	Sequence 2(A-C-B)	Sequence 3(B-C-A)
Started	19	20	18
Completed	16	19	17
Not completed	3	1	1
technical problems	1	-	-
Physician decision	-	-	-
subject/guardian decision	1	-	-
Adverse event, non-fatal	1	1	1
Non-compliance with study treatment	-	-	-

Number of subjects in period 1	Sequence 4(B-A-C)	Sequence 5(C-A-B)	Sequence 6(C-B-A)
Started	20	20	19
Completed	17	20	18
Not completed	3	0	1
technical problems	-	-	-
Physician decision	1	-	-
subject/guardian decision	-	-	-
Adverse event, non-fatal	1	-	-
Non-compliance with study treatment	1	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	116	116	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	98	98	
From 65-84 years	18	18	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	49.5		
standard deviation	± 14	-	
Sex: Female, Male Units: Subjects			
Female	55	55	
Male	61	61	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	9	9	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	106	106	
More than one race	0	0	
Unknown or Not Reported	0	0	

Subject analysis sets

Subject analysis set title	All participants
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomized to one of six treatment sequences

Subject analysis set title	QVM149 150/50/160 µg o.d.
Subject analysis set type	Full analysis

Subject analysis set description:

QVM149 150/50/160 µg o.d. vs

salmeterol/fluticasone 50/500 µg b.i.d

Subject analysis set title	QVM149 150/50/80 µg o.d.
Subject analysis set type	Full analysis

Subject analysis set description:

QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.

Subject analysis set title	Salmeterol/fluticasone 50/500 µg b.i.d.
Subject analysis set type	Full analysis

Subject analysis set description:

Salmeterol/fluticasone 50/500 µg b.i.d.

Reporting group values	All participants	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.
Number of subjects	116	112	115
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	98		
From 65-84 years	18		
85 years and over			
Age Continuous Units: years			
arithmetic mean	49.5		
standard deviation	± 14	±	±
Sex: Female, Male Units: Subjects			
Female	55		
Male	61		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	9		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	106		
More than one race	0		
Unknown or Not Reported	0		

Reporting group values	Salmeterol/fluticasone 50/500 µg b.i.d.		
Number of subjects	111		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	±		
Sex: Female, Male Units: Subjects			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Sequence 1 (A-B-C)
Reporting group description: QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.	
Reporting group title	Sequence 2(A-C-B)
Reporting group description: QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d;	
Reporting group title	Sequence 3(B-C-A)
Reporting group description: QVM149 150/50/160 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/80 µg o.d	
Reporting group title	Sequence 4(B-A-C)
Reporting group description: QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d	
Reporting group title	Sequence 5(C-A-B)
Reporting group description: salmeterol/fluticasone FDC 50/500 µg b.i.d; QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d	
Reporting group title	Sequence 6(C-B-A)
Reporting group description: salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d	
Subject analysis set title	All participants
Subject analysis set type	Full analysis
Subject analysis set description: All participants randomized to one of six treatment sequences	
Subject analysis set title	QVM149 150/50/160 µg o.d.
Subject analysis set type	Full analysis
Subject analysis set description: QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d	
Subject analysis set title	QVM149 150/50/80 µg o.d.
Subject analysis set type	Full analysis
Subject analysis set description: QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.	
Subject analysis set title	Salmeterol/fluticasone 50/500 µg b.i.d.
Subject analysis set type	Full analysis
Subject analysis set description: Salmeterol/fluticasone 50/500 µg b.i.d.	

Primary: Peak FEV1 (mL) defined as the highest bronchodilatory effect on FEV1 during a period of 5 min to 4 h after the last evening dose of each treatment period

End point title	Peak FEV1 (mL) defined as the highest bronchodilatory effect on FEV1 during a period of 5 min to 4 h after the last evening dose of each treatment period
End point description: The highest bronchodilator effect on FEV1 during a period of 5 min to 4 h after the last evening dose of each treatment period . To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma	
End point type	Primary
End point timeframe: 3 weeks	

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[1]	115[2]		
Units: Liters				
least squares mean (confidence interval 95%)	0.172 (0.137 to 0.208)	0.159 (0.123 to 0.195)		

Notes:

[1] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[2] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.

Statistical analyses

Statistical analysis title	Peak FEV1
Comparison groups	QVM149 150/50/160 µg o.d. v QVM149 150/50/80 µg o.d.
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.172
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	0.208

Secondary: Mean FEV1 over 24 h after 21 days of treatment in relation to evening dose

End point title	Mean FEV1 over 24 h after 21 days of treatment in relation to evening dose

End point description:

To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment at -45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.

End point type	Secondary

End point timeframe:

-45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min at 3 weeks

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[3]	115[4]		
Units: Liters				
least squares mean (confidence interval 95%)				
-45 min	0.1306 (0.0803 to 0.1810)	0.0708 (0.0204 to 0.1213)		
-15 min	0.1188 (0.0715 to 0.1660)	0.0794 (0.0320 to 0.1269)		
5 min	0.1376 (0.0946 to 0.1806)	0.1143 (0.0712 to 0.1575)		
15 min	0.1525 (0.0991 to 0.2058)	0.0965 (0.0429 to 0.1502)		
30 min	0.1588 (0.1160 to 0.2015)	0.1218 (0.0789 to 0.1647)		
1 h	0.1524 (0.1115 to 0.1933)	0.1427 (0.1016 to 0.1838)		
2 h	0.1790 (0.1364 to 0.2215)	0.1752 (0.1324 to 0.2180)		
3 h	0.1699 (0.1264 to 0.2135)	0.1424 (0.0986 to 0.1862)		
4 h	0.1651 (0.1172 to 0.2130)	0.1401 (0.0920 to 0.1882)		
8 h	0.1883 (0.1438 to 0.2328)	0.1632 (0.1183 to 0.2080)		
10 h	0.2091 (0.1603 to 0.2579)	0.1887 (0.1396 to 0.2379)		
11h 55 min	0.2201 (0.1718 to 0.2685)	0.1800 (0.1313 to 0.2287)		
14 h	0.1475 (0.1029 to 0.1921)	0.1187 (0.0737 to 0.1636)		
18 h	0.1017 (0.0577 to 0.1457)	0.0744 (0.0300 to 0.1188)		
21 h	0.0980 (0.0517 to 0.1442)	0.0856 (0.0389 to 0.1322)		
23 h 15 min	0.1289 (0.0873 to 0.1705)	0.1096 (0.0675 to 0.1516)		
23 h 45 min	0.1054 (0.0638 to 0.1470)	0.0810 (0.0389 to 0.1230)		

Notes:

[3] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[4] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.

Statistical analyses

No statistical analyses for this end point

Secondary: FVC over 24 h after 21 days of treatment in relation to evening dose

End point title	FVC over 24 h after 21 days of treatment in relation to evening dose

End point description:

To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment at -45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.

End point type	Secondary

End point timeframe:

-45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min at 3 weeks

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	112[5]	115[6]	111[7]	
Units: Liters				
arithmetic mean (standard deviation)				
-45min	3.9046 (± 1.03169)	3.8538 (± 0.98086)	3.7626 (± 1.00067)	
-15min	3.8743 (± 1.04318)	3.8571 (± 0.97420)	3.7230 (± 0.94180)	
5min	3.8656 (± 0.99877)	3.8976 (± 1.00323)	3.7536 (± 0.93696)	
15min	3.8669 (± 0.98489)	3.8971 (± 0.96840)	3.7290 (± 0.94033)	
30min	3.8700 (± 0.99289)	3.9002 (± 0.99091)	3.7695 (± 0.96026)	
1h	3.8756 (± 0.99978)	3.8993 (± 0.99141)	3.7530 (± 0.97083)	
2h	3.8698 (± 0.99623)	3.8985 (± 0.99369)	3.7629 (± 0.97164)	
3h	3.8576 (± 0.98598)	3.8766 (± 0.97806)	3.7575 (± 0.96899)	
4h	3.8744 (± 0.99833)	3.8627 (± 0.95673)	3.7629 (± 0.98205)	
8h	3.9020 (± 0.98241)	3.9217 (± 0.99184)	3.7683 (± 1.00410)	
10h	3.8976 (± 0.98360)	3.9504 (± 0.99286)	3.7809 (± 0.98213)	
11h 55min	3.9271 (± 0.98924)	3.9405 (± 1.00198)	3.7911 (± 0.99102)	

14h	3.9091 (± 1.00241)	3.9210 (± 0.97942)	3.8089 (± 1.02918)	
18h	3.8675 (± 0.95725)	3.9151 (± 1.02198)	3.7824 (± 0.98395)	
21h	3.8438 (± 1.00672)	3.8694 (± 0.98786)	3.7680 (± 1.00768)	
23h 15min	3.7977 (± 0.97550)	3.8673 (± 0.99915)	3.7395 (± 1.01764)	
23h 45min	3.8034 (± 0.99036)	3.8603 (± 0.98502)	3.7431 (± 1.00668)	

Notes:

[5] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[6] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[7] - Salmeterol/fluticasone 50/500 µg b.i.d.

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1/FVC ratio over 24 h after 21 days of treatment in relation to evening dose

End point title	FEV1/FVC ratio over 24 h after 21 days of treatment in relation to evening dose

End point description:

To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment at -45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.

End point type	Secondary

End point timeframe:

-45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min at 3 weeks

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	112[8]	115[9]	111[10]	
Units: Liters				
arithmetic mean (standard deviation)				
-45min	0.6701 (± 0.10880)	0.6612 (± 0.10358)	0.6527 (± 0.10867)	
-15min	0.6707 (± 0.10646)	0.6669 (± 0.10422)	0.6539 (± 0.10526)	
5min	0.6788 (± 0.10300)	0.6754 (± 0.10370)	0.6563 (± 0.10639)	
15min	0.6873 (± 0.10126)	0.6778 (± 0.10734)	0.6560 (± 0.10823)	
30min	0.6878 (± 0.10137)	0.6844 (± 0.10699)	0.6573 (± 0.10552)	
1h	0.6900 (± 0.09764)	0.6895 (± 0.09940)	0.6632 (± 0.10403)	
2h	0.6939 (± 0.09629)	0.6932 (± 0.10073)	0.6647 (± 0.10413)	
3h	0.6968 (± 0.10159)	0.6890 (± 0.10052)	0.6634 (± 0.10436)	

4h	0.6897 (± 0.10060)	0.6879 (± 0.09733)	0.6605 (± 0.10419)	
8h	0.6842 (± 0.10782)	0.6802 (± 0.11349)	0.6492 (± 0.10814)	
10h	0.6916 (± 0.10550)	0.6858 (± 0.10468)	0.6489 (± 0.11155)	
11h 55min	0.6853 (± 0.10672)	0.6791 (± 0.10656)	0.6482 (± 0.10810)	
14h	0.6846 (± 0.10842)	0.6848 (± 0.10450)	0.6567 (± 0.11048)	
18h	0.6801 (± 0.09943)	0.6741 (± 0.10240)	0.6546 (± 0.10369)	
21h	0.6790 (± 0.10890)	0.6785 (± 0.10387)	0.6562 (± 0.10729)	
23h 15min	06821 (± 0.10386)	0.6791 (± 0.09986)	0.6548 (± 0.10423)	
23h 45min	0.6782 (± 0.10457)	0.6776 (± 0.10111)	0.6537 (± 0.10934)	

Notes:

[8] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[9] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.

[10] - Salmeterol/fluticasone 50/500 µg b.i.d.

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 AUC 5 min - 1 h (Day 21) FEV1 AUC 5 min - 4 h (Day 21) and FEV1 AUC 5 min - 23 h 45 min (Day 21)

End point title	FEV1 AUC 5 min - 1 h (Day 21) FEV1 AUC 5 min - 4 h (Day 21) and FEV1 AUC 5 min - 23 h 45 min (Day 21)

End point description:

To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/ fluticasone FDC by measuring standardized FEV1 AUCs after 3 weeks of treatment respective period.

End point type	Secondary

End point timeframe:

3 weeks

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[11]	115[12]		
Units: Liters				
least squares mean (confidence interval 95%)				
FEV1 AUC 5 min - 1 h	0.160 (0.120 to 0.201)	0.131 (0.090 to 0.172)		
FEV1 AUC 5 min - 4 h	0.177 (0.141 to 0.213)	0.159 (0.123 to 0.195)		
FEV1 AUC 5 min - 23 h 45 min	0.163 (0.128 to 0.197)	0.138 (0.103 to 0.173)		

Notes:

[11] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[12] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

Statistical analyses

No statistical analyses for this end point

Secondary: Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose)

End point title	Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose)

End point description:

To evaluate post-dose trough bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment in the respective treatment period.

End point type	Secondary

End point timeframe:

3 weeks

End point values	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112[13]	115[14]		
Units: Liters				
least squares mean (confidence interval 95%)	0.124 (0.086 to 0.161)	0.105 (0.067 to 0.143)		

Notes:

[13] - QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

[14] - QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d

Statistical analyses

Statistical analysis title	Trough FEV1
Comparison groups	QVM149 150/50/160 µg o.d. v QVM149 150/50/80 µg o.d.
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.161

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	QVM149 150/50/160 µg o.d.
Reporting group description:	
QVM149 150/50/160 µg o.d.	
Reporting group title	Salmeterol/fluticasone 50/500 µg b.i.d.
Reporting group description:	
Salmeterol/fluticasone 50/500 µg b.i.d.	
Reporting group title	QVM149 150/50/80 µg o.d.
Reporting group description:	
QVM149 150/50/80 µg o.d.	

Serious adverse events	QVM149 150/50/160 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.	QVM149 150/50/80 µg o.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 112 (0.00%)	0 / 111 (0.00%)	0 / 115 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	QVM149 150/50/160 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.	QVM149 150/50/80 µg o.d.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 112 (12.50%)	21 / 111 (18.92%)	18 / 115 (15.65%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 112 (8.93%)	13 / 111 (11.71%)	10 / 115 (8.70%)
occurrences (all)	12	15	11
Respiratory, thoracic and mediastinal disorders			
Dysphonia			

subjects affected / exposed	6 / 112 (5.36%)	6 / 111 (5.41%)	1 / 115 (0.87%)
occurrences (all)	6	6	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 111 (0.90%)	0 / 115 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 112 (2.68%)	4 / 111 (3.60%)	7 / 115 (6.09%)
occurrences (all)	3	4	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2018	Modification of the inclusion criterion for duration of baseline ICS/LABA requirements from 1 year to 3 months. This was based on investigator feedback from real-world asthma populations and intended to address evolving treatment patterns, whereby patient medications are more rapidly up-titrated in response to symptoms. This would help identify previously ineligible patients who may potentially benefit from treatment with LAMA as add-on therapy to existing ICS/LABA treatment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: