Sponsor

Generic Drug Name

QVM149 (indacaterol acetate, glycopyrronium bromide, and mometasone furoate)

Trial Indication(s)

Asthma

Protocol Number

CQVM149B2208

Protocol Title

A randomized, double-blind, double-dummy, active-controlled, 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

Clinical Trial Phase

Phase of Drug Development

II

Study Start/End Dates

Study Start Date: January 2017 (Actual)

Primary Completion Date: August 2018 (Actual)
Study Completion Date: August 2018 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a confirmatory, randomized, double-blind, double-dummy, active-controlled, three-period complete cross-over study. During the two-week screening period, patients were abstained from the usage of any asthma medication before screening lung function assessments. Patients were allowed to use their previous asthma medication between screening spirometry and randomization. All previous asthma medications were stopped at randomization prior to study treatment administration. Short-acting beta-2-agonist (SABA) bronchodilators were provided to each patient to use as rescue medication throughout the study. At the end of the screening period, patients were randomized to one of the six possible treatment sequences (3 treatments and 3 periods in the ratio of 1:1:1:1:1:1), each consisting of three double-blind, double-dummy treatment periods of 21 days (cross-over design). The treatments were A= QVM149 150/50/80 µg o.d.; B= QVM149 150/50/160 µg o.d.; C= salmeterol/fluticasone FDC 50/500 µg b.i.d. There was no washout period between treatment periods. Each treatment sequence had approximately 19 patients. Procedures in all treatment periods were identical.

Centers

12 centers in 6 countries: Netherlands(1), Germany(5), Bulgaria(1), United Kingdom(1), China(3), Romania(1)

Objectives:

The primary objective- was 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.

The secondary objective- was to evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment in terms of: Trough FEV1, Standardized Forced expiratory volume in one second (FEV1) area under the curves (AUCs), Forced Vital Capacity (FVC), and the FEV1/FVC ratio.

To evaluate the safety and tolerability of each dose of QVM149 and salmeterol/ fluticasone FDC when administered for 3 weeks: hematology, blood chemistry, urine analysis, vital signs and electrocardiogram (ECG), adverse events (AE).

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

The investigational drug, QVM149 150/50/80 µg, 150/50/160 µg and salmeterol xinafoate/fluticasone propionate 50/500 µg as well as their respective matching placebos were prepared by Novartis and supplied to the investigator as single blind patient kits with a tear off-label.

Statistical Methods

The primary endpoint is the peak FEV1 (L) defined as the highest bronchodilatory

effect on FEV1 during a period of 5 min to 4 h after the last evening dose of the preceding 3-week

treatment period. The following hypothesis was tested for each of QVM149 doses versus

salmeterol/fluticasone separately:

H0: There is no difference in terms of the peak FEV1 after 21 days of treatment between:

The QVM149 high dose (150/50/160 µg) and salmeterol/fluticasone or

The QVM149 mid dose (150/50/80 µg) and salmeterol/fluticasone

H1: There is a difference in terms of the peak FEV1 after 21 days of treatment between:

QVM149 high dose (150/50/160 µg) and salmeterol/fluticasone and
QVM149 mid dose (150/50/80 µg) and salmeterol/fluticasone
Each test was conducted at a one-sided 2.5% level.
The primary variable was analyzed using a linear mixed model. The model included period, treatment, and sequence as fixed effect factors and patient as a random effect. Restricted maximum likelihood method was used. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. No adjustment for multiplicity was planned because both tests were required to be positive.
The pairwise treatment differences of each QVM149 dose versus salmeterol/fluticasone along with the corresponding 2-sided 95% confidence intervals (CI) was presented. In addition, the difference between adjusted means and the corresponding two-sided 95% CI for QVM149 high versus medium doses were estimated.
The secondary endpoints standardized AUC in FEV1 (5 min-23 h 45 min), in FEV1 (5 min -1 h), in FEV1 (5 min - 4 h) and trough FEV1 was analyzed by fitting the same model as described for the primary endpoint.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria
• Male and female adult patients ≥ 18 years old and ≤ 75 years.
• Patients with a documented physician diagnosis of asthma for a period of at least 12 months prior to Visit 1 (Screening).
• Patients who have used ICS and LABA combinations for asthma for at least 3 month and at a stable medium or high dose of ICS for at least 1 month prior to Visit 1 (Screening).
• Pre-bronchodilator FEV1 of < 80 % of the predicted normal value at screening Visit 1 (spirometry will not be repeated at baseline prior to randomization).
• Patients who demonstrate an increase in FEV1 of ≥ 12 % and 200 mL after administration of 400 µg salbutamol/360 µg albuterol (or equivalent do se) at Visit 1 (Screening). All patients must perform a reversibility test at Visit 1 (Screening). If reversibility is not demonstrated at Visit 1 (Screening), then, reversibility testing may be repeated once during the screening period.
• If reversibility is not demonstrated at Visit 1 (retesting allowed once), patients must be screen failed. Spacer devices are not

permitted during reversibility testing
Key Exclusion criteria
• Patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1
• Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1
• Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or severe renal impairment or urinary retention
• Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Visit 1
• Patients with any chronic conditions affecting the upper respiratory tract
• Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
• Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c >9% at screening).
• Patients who have a clinically significant ECG abnormality at Visit 1
• Patients with a history of hypersensitivity or intolerance to any of the study drugs (including excipients)
• Patients with narcolepsy and/or insomnia.
• Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 2 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 2 but expected to change throughout the course of the study.
• Pregnant or nursing (lactating) women
• Women of child-bearing potential must use Highly effective contraception methods
• Patients who have discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason.
• History of paradoxical bronchospasm in response to inhaled medicines.
• Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
• Patient with a serum potassium level below the laboratory limit of normal at screening.

Participant Flow Table

Overall Study

	Sequence 1 (A-B-C)	Sequence 2(A-C-B)	Sequence 3(B-C-A)	Sequence 4(B-A-C)	Sequence 5(C-A-B)	Sequence 6(C-B-A)	Total
Arm/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.	QVM149 150/50/80 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d;	QVM149 150/50/160 µg o.d; salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/80 µg o.d	QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d; salmeterol/fluticaso	salmeterol/fluticasone FDC 50/500 µg b.i.d; QVM149 150/50/80 µg o.d; QVM149 150/50/160 µg o.d	salmeterol/fluticasone FDC 50/500 µg b.i.d.; QVM149 150/50/160 µg o.d; QVM149 150/50/80 µg o.d	

				ne FDC 50/500 µg b.i.d			
Started	19	20	18	20	20	19	116
Completed	16	19	17	17	20	18	107
Not Completed	3	1	1	3	0	1	9
technical problems	1	0	0	0	0	0	1
Adverse Event	1	1	1	1	0	0	4
subject/guardian decision	1	0	0	0	0	0	1
Non-compliance with study treatment	0	0	0	1	0	1	2
Physician Decision	0	0	0	1	0	0	1

Baseline Characteristics

	All participants	**Total**
Arm/Group Description	All participants randomized to one of six treatment sequences	
Number of Participants [units: participants]	116	116
Age Continuous (units: Years) Mean ± Standard Deviation		

	49.5±14	
Sex: Female, Male (units:) Count of Participants (Not Applicable)		
Female	55	55
Male	61	61
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)		
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

Summary of Efficacy

Primary Outcome Result(s)

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
(Time Frame: 3 weeks)

	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.
Arm/Group Description	QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500	QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.
Number of Participants Analyzed [units: participants]	112	115
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 (units: Liters) Least Squares Mean (95% Confidence Interval)		
	0.172 (0.137 to 0.208)	0.159 (0.123 to 0.195)

Statistical Analysis

Groups	QVM149 150/50/160 µg o.d.
P Value	<0.0001
Method	Mixed Models Analysis
Mean Difference (Final Values)	0.172
95 % Confidence Interval 2-Sided	0.137 to 0.208

Secondary Outcome Result(s)

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

(Time Frame: -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)

	QVM149 150/50/160	QVM149 150/50/80
Arm/Group Description	QVM149 150/50/160 µg o.d. vs. salmeterol/fluticasone 50/500 µg b.i.d	QVM149 150/50/80 µg o.d. vs. salmeterol/fluticasone 50/500 µg b.i.d.
Number of Participants Analyzed [units: participants]	112	114
Mean FEV1 over 24 h after 21 days of treatment in relation to evening dose (units: Liters) Least Squares Mean (95% Confidence Interval)		
-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)

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

(Time Frame: -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)

	QVM149 150/50/160	QVM149 150/50/80	Salmeterol/fluticasone
Arm/Group Description	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg BID
Number of Participants Analyzed [units: participants]	112	115	111

FVC over 24 h after 21 days of treatment in relation to evening dose
(units: Liters)
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

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

(Time Frame: -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)

	QVM149 150/50/160	**QVM149 150/50/80**	**Salmeterol/fluticasone**
Arm/Group Description	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg BID
Number of Participants Analyzed [units: participants]	112	115	111
FEV1/FVC ratio over 24 h after 21 days of treatment in relation to evening dose (units: Liters) 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

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)

(Time Frame: 3 weeks)

	QVM149 150/50/160 µg o.d.	**QVM149 150/50/80 µg o.d.**
Arm/Group Description	QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.	QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.
Number of Participants Analyzed [units: participants]	112	115

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)

(units: Liters) Least Squares Mean (95% Confidence Interval)		
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)

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

(Time Frame: 3 weeks)

	QVM149 150/50/160	**QVM149 150/50/80 µg o.d.**
Arm/Group Description	QVM149 150/50/160 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.	QVM149 150/50/80 µg o.d. vs salmeterol/fluticasone 50/500 µg b.i.d.
Number of Participants Analyzed [units: participants]	112	115
Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose) (units: Liters) Least Squares Mean (95% Confidence Interval)		
	0.124 (0.086 to 0.161)	0.105 (0.067 to 0.143)

Statistical Analysis

Groups	QVM149 150/50/160
P Value	<0.0001

Method	Mixed Models Analysis
Mean Difference (Final Values)	0.124
95 % Confidence Interval 2-Sided	0.086 to 0.161

Summary of Safety

Safety Results

All-Cause Mortality

	QVM149 150/50/160 µg o.d. N = 112	QVM149 150/50/80 µg o.d. N = 115	Salmeterol/fluticasone 50/500 µg b.i.d. N = 111
Arm/Group Description	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Up to 22 days
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	QVM149 150/50/160 µg o.d. N = 112	**QVM149 150/50/80 µg o.d. N = 115**	**Salmeterol/fluticasone 50/500 µg b.i.d. N = 111**
Arm/Group Description	QVM149 150/50/160 µg o.d.	QVM149 150/50/80 µg o.d.	Salmeterol/fluticasone 50/500 µg b.i.d.
Total participants affected	14 (12.50%)	18 (15.65%)	21 (18.92%)
Infections and infestations			
Nasopharyngitis	3 (2.68%)	7 (6.09%)	4 (3.60%)
Musculoskeletal and connective tissue disorders			
Back pain	0 (0.00%)	0 (0.00%)	1 (0.90%)
Nervous system disorders			
Headache	10 (8.93%)	10 (8.70%)	13 (11.71%)
Respiratory, thoracic and mediastinal disorders			
Dysphonia	6 (5.36%)	1 (0.87%)	6 (5.41%)

Other Relevant Findings

None

Conclusion:

The lung function benefit with QVM149 150/50/160 µg o.d. (high dose) and 150/50/80 µg o.d. (medium dose) treatment for 21 days was demonstrated to be superior to salmeterol/fluticasone 50/500 µg b.i.d. in terms of peak FEV1. An increase of approximately 0.172 L and 0.159 L in peak FEV1 with QVM149 high dose and medium dose, respectively, compared to salmeterol/fluticasone ($p<0.0001$) was observed.
Both QVM149 doses showed improved treatment effect on other endpoints including standardized FEV1AUCs, trough FEV1, mean FEV1 measured over 24 h post-dose, and PEF.
While both QVM149 doses were superior to salmeterol/fluticasone, rescue medication use patterns and numerical dose-ordering of lung function benefits may suggest an added benefit of QVM149 150/50/160 µg as compared to QVM149 150/50/80 µg.
Both QVM149 doses were safe and well-tolerated with no relevant difference between QVM149 doses and salmeterol/fluticasone 50/500 µg b.i.d., no SAEs, no deaths and no new safety signals were detected. Adverse events were in line with the underlying disease and/or the known safety profile of monotherapy components of QVM149

Date of Clinical Trial Report

19-Dec-2018