NOVARTIS

Clinical Trial Results Website

Sponsor

Generic Drug Name

QVM149

Trial Indication(s)

Asthma.

Protocol Number

CQVM149B2209

Protocol Title

A randomized, double-blind, repeat dose cross-over study to assess the bronchodilator effects of once daily QVM149 following morning or evening dosing for 14 days compared to placebo in patients with asthma

Clinical Trial Phase

II

Phase of Drug Development

III

Study Start/End Dates

Study Start Date: June 2017 (Actual)

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

Reason for Termination (If applicable)

Study Design/Methodology

The QVM149B2209 is a six treatments sequence, three-period cross-over study in asthma patients. The study consisted of a 14-day screening period, followed by a 14-day run-in period, and 3 treatment epochs, with a minimum duration of 14 days each followed by a wash-out period (for the 2 first treatment periods) of 14 to 21 days duration. The total duration of the study was approximately 13 weeks (minimum) to 19 weeks (maximum) for each patient.

Centers

7 centers in 3 countries: Netherlands(1), Germany(5), United Kingdom(1)

Objectives:

Primary Objective:

- To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo.

Secondary Objectives:

- To investigate the potential influence of time of dosing (morning or evening) on trough FEV1 of once daily orally inhaled QVM149 compared to placebo.
- To investigate the potential influence of time of dosing (morning or evening), on peak expiratory flow (PEF) rate of once daily orally inhaled QVM149 compared to placebo (all administered via the Concept1 inhalation device).
- To evaluate safety and tolerability of QVM149 when dosed in the morning or in the evening in patients with asthma during two weeks of treatment in each treatment period.

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

Study drug/ Unit dose	Appearance	Packaging	Formulation
QVM149 and Concept1 Inhaler/ 150/50/80µg	Hard capsules	Provided as single blinded supplies including Concept1 devices	Capsules with powder for Inhalation
Placebo to QVM149 and Concept1 Inhaler/ 0µg	Hard capsules	Provided as single blinded supplies including Concept1 devices	Capsules with powder for Inhalation
Placebo to QVM149 and Concept 1 Inhaler as training kit/ 0µg	Hard capsules	Blister +Inhaler	Capsules with powder for Inhalation
Concept1 device/ NA	Single-dose dry powder inhaler	Inhaler	NA

Statistical Methods

Primary variable

The primary variable, FEV1 weighted mean (0- 24 h) (AUC0-24h), was analyzed using a linear mixed effect model. The model included period, treatment (QVM149 morning, QVM149 evening, placebo), and sequence as fixed effect factors. The patient effect was assumed to be random.

A pre-planned supportive analysis was performed in which repeated measures of FEV1 over 24 h after Day 14 evening dose were analyzed to provide average treatment effect on the overall bronchodilator profile over 0-24 h. The inference was valid under ‘Missing at Random.

A sensitivity analysis was performed on a subset of patients, where patients having drug administered

outside of the allowed time window on Day 14 or Day 15 were excluded. Spirometry data assessed outside of the allowed time window were also excluded.

A subgroup analysis was planned to be performed on a group of patients based on their compliance of study medication within 7 days before the spirometry assessment. The analysis could not be performed as there were only two patients with <80% treatment compliance who discontinued prematurely from the study.

Secondary Variables

The a.m. and p.m. trough FEV1 (mL) were analyzed using the same model as for the primary endpoint as described above. The model included period, treatment (QVM149 morning, QVM149 evening, placebo), and sequence as fixed effect factors. The patient effect was assumed to be random.

PEF (L/min) was analyzed separately for morning and evening values. The morning/evening PEF (L/min) were averaged between Day 2 to 14 of each treatment period for each patient and was analyzed using the same model as for the primary endpoint as described above.

A post hoc supportive analysis was performed to provide a direct comparison of the residual effect of morning and evening dosing on FEV1 as captured through FEV1 (L) measured after approximately 24 h of last p.m. dose or penultimate a.m. dose. A similar post hoc analysis was also performed to provide a direct comparison of potential influence of a.m. vs p.m. dosing on average PEF over Day 2 – Day 14.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

Patients with a documented physician diagnosis of asthma and who additionally meet the following criteria:

− Patients receiving daily treatment with an inhaled corticosteroid at a low or medium daily dose

− On a stable regimen for at least 4 weeks prior to screening.

- Pre-bronchodilator FEV1 ≥ 60 % and < 100% of the predicted normal value for the patient during screening.

- Patients who demonstrate an increase in FEV1 of ≥ 12 % and ≥ 200 mL after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Screening. All patients must perform a reversibility test at Screening.

- At screening, and baseline (day 1 pre-dose time) of the first treatment period, vital signs (systolic and diastolic blood pressure and

pulse rate) will be assessed in the sitting position and again in the standing position as outlined in the SOM. Sitting and standing vital signs should be within the following ranges:
− oral body temperature between 35.0-37.5 °C
− systolic blood pressure, 90-159 mmHg
− diastolic blood pressure, 50-99 mmHg
− pulse rate, 40-90 bpm
- Hypertensive patients must have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial.
- Patients must weigh at least 50 kg at screening to participate in the study, and must have a body mass index (BMI) within the range of 18 to 40 kg/m2.

Exclusion Criteria:

- Contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the drugs of a similar class
- Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 1 year of Screening.
- Patients who have had previous intubation for a severe asthma ttack/exacerbation.
- Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
- History of paradoxical bronchospasm in response to inhaled medicines.
- Patients who during the run-in period prior to randomization require the use of ≥12 puffs / 24 hours of rescue medication for 48 hours (over two consecutive days) or who have a decline in PEF from the reference PEFof ≥ 30% for 6 consecutive scheduled PEF readings
- Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).

Participant Flow Table

Period 1

	Sequence 1	Sequence 2	Sequence 3	Sequence 4	Sequence 5	Sequence 6
Started	7	6	6	6	6	6
Completed	7	6	6	4	6	6
Not Completed	0	0	0	2	0	0

Subject/Guardian Decision	0	0	0	2	0	0

Period 2

	Sequence 1	Sequence 2	Sequence 3	Sequence 4	Sequence 5	Sequence 6
Started	7	6	6	4	6	6
Completed	7	6	6	4	6	6
Not Completed	0	0	0	0	0	0

Period 3

	Sequence 1	Sequence 2	Sequence 3	Sequence 4	Sequence 5	Sequence 6
Started	7	6	6	4	6	6
Completed	7	5	6	4	6	6
Not Completed	0	1	0	0	0	0
Adverse Event	0	1	0	0	0	0

Baseline Characteristics

	All participants	Total
Number of Participants [units: participants]	37	37

Age Continuous (units: Years) Mean ± Standard Deviation		
	43.5±14.04	
Sex: Female, Male (units:) Count of Participants (Not Applicable)		
Female	16	16
Male	21	21
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)		
American Indian or Alaska Native	0	0
Asian	0	0
Native Hawaiian or Other Pacific Islander	0	0
Black or African American	0	0
White	35	35
More than one race	0	0
Unknown or Not Reported	2	2

Summary of Efficacy

Primary Outcome Result(s)

FEV1 standardized Area Under the Curve (AUC 0-24h) after last evening dose of 14-day treatment period

	QVM149 am	QVM149 pm	Placebo
Number of Participants Analyzed [units: participants]	30	30	33
FEV1 standardized Area Under the Curve (AUC 0-24h) after last evening dose of 14-day treatment period (units: Liters) Least Squares Mean ± Standard Error			
	3.4305 ± 0.15242	3.4361 ± 0.15213	2.8209 ± 0.15259

Statistical Analysis

Groups	QVM149 am, Placebo	
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
Mean Difference (Net)	0.6096	
90 % Confidence Interval 2-Sided	0.5380 to 0.6811	

Statistical Analysis

Groups	QVM149 pm, Placebo	
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
	0.6152	
90 % Confidence Interval 2-Sided	0.5437 to 0.6868	

Statistical Analysis

Groups	QVM149 am, QVM149 pm	
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
	-0.0057	
90 % Confidence Interval 2-Sided	-0.0760 to 0.0647	

Secondary Outcome Result(s)

Trough FEV1 after 24h

	QVM149 am	QVM149 pm	Placebo
Number of Participants Analyzed [units: participants]	35	35	36
Trough FEV1 after 24h (units: Liters) Least Squares Mean ± Standard Error			
	3.3731 ± 0.15037	3.4871 ± 0.15041	2.7524 ± 0.15120

Statistical Analysis

Groups	QVM149 am, Placebo	
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
Mean Difference (Net)	0.6206	
90 % Confidence Interval 2-Sided	0.5335 to 0.7077	

Statistical Analysis

Groups	QVM149 pm, Placebo

Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
	0.7347	
90 % Confidence Interval 2-Sided	0.6469 to 0.8225	

Statistical Analysis

Groups	QVM149 am, QVM149 pm	
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
	-0.1141	
90 % Confidence Interval 2-Sided	-0.1970 to -0.0311	

Peak expiratory flow (PEF)

	QVM149 am	QVM149 pm	Placebo

Number of Participants Analyzed [units: participants]	35	35	36
Peak expiratory flow (PEF) (units: L/min) Least Squares Mean ± Standard Error			
Morning average PEF	489.6 ± 19.77	504.4 ± 19.78	417.5 ± 19.73
Evening average PEF	522.0 ± 19.71	507.7 ± 19.71	449.0 ± 19.67

Statistical Analysis

Groups	QVM149 am, Placebo	Morning average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
Mean Difference (Net)	72.1	
90 % Confidence Interval 2-Sided	61.3 to 82.9	

Statistical Analysis

Groups	QVM149 pm, Placebo	Morning average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting

		confidence interval of treatment difference.’
Method	Mixed Models Analysis	
	86.9	
90 % Confidence Interval 2-Sided	76.1 to 97.8	

Statistical Analysis

Groups	QVM149 am, QVM149 pm	Morning average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.’
Method	Mixed Models Analysis	
	-14.8	
90 % Confidence Interval 2-Sided	-25.6 to -4.1	

Statistical Analysis

Groups	QVM149 am, Placebo	Evening average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.’

Method	Mixed Models Analysis
	73.1
90 % Confidence Interval 2-Sided	61.9 to 84.2

Statistical Analysis

Groups	QVM149 pm, Placebo	Evening average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'
Method	Mixed Models Analysis	
	58.7	
90 % Confidence Interval	47.5 to 69.9	

Statistical Analysis

Groups	QVM149 am, QVM149 pm	Evening average PEF
Non-Inferiority/Equivalence Test		A hypothesis test is not planned for this study, inferences are to be performed by interpreting confidence interval of treatment difference.'

Method	Mixed Models Analysis
	14.4
90 % Confidence Interval 2-Sided	3.3 to 25.5

Summary of Safety

Safety Results

All-Cause Mortality

	QVM149 a.m. N = 35	QVM149 p.m. N = 35	Placebo N = 36
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	Treatment-emergent adverse events
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	QVM149 a.m. N = 35	QVM149 p.m. N = 35	Placebo N = 36
Total participants affected	11 (31.43%)	13 (37.14%)	16 (44.44%)
Infections and infestations			
Nasopharyngitis	2 (5.71%)	2 (5.71%)	5 (13.89%)
Nervous system disorders			
Headache	5 (14.29%)	3 (8.57%)	7 (19.44%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (2.86%)	2 (5.71%)	1 (2.78%)
Dysphonia	2 (5.71%)	3 (8.57%)	1 (2.78%)
Oropharyngeal pain	3 (8.57%)	4 (11.43%)	2 (5.56%)

Other Relevant Findings

None

Conclusion:

Morning and evening dosing of QVM149 150/50/80 µg improved weighted mean FEV1 (0-24 h) by 0.6096 L and 0.6152 L respectively over placebo after 14 days of treatment. There was no clinically meaningful difference in weighted mean FEV1 (0.0057 L) over 24 h between morning and evening dosing of once daily orally inhaled QVM149 150/50/80 µg.

Results for the secondary endpoints trough FEV1 and PEF are consistent with those for the primary endpoint substantiating that there is no difference between QVM149 morning vs. evening dosing.
The magnitude of the effect of QVM149 a.m. or QVM149 p.m. dosing compared to placebo suggests that QVM149 elicits substantial bronchodilation in asthma patients.
The safety/tolerability profiles of QVM149 are comparable between morning and evening dosing and are similar to placebo. There were no findings that suggest a change to the known safety profile of QVM149.
These results demonstrate that QVM149 is effective irrespective of the time of dosing during the day and therefore, that QVM149 can be administered effectively and safely either in the morning or in the evening.

Date of Clinical Trial Report

11-Oct-2018