Clinical trial results:
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

Summary

EudraCT number	2017-000644-17
Trial protocol	NL DE GB
Global end of trial date	24 February 2018

Results information

Result version number	v1 (current)
This version publication date	10 March 2019
First version publication date	10 March 2019

Trial information

Trial identification

Sponsor protocol code	CQVM149B2209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03108027
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Swaziland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	24 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

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	26 June 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	Germany: 30
Country: Number of subjects enrolled	Netherlands: 7
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	35
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a randomized, placebo-controlled, double-blind, six-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 three treatment periods.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1

Arm description:

Patients received in a sequential order the following interventional treatments: A,B and C.

Arm type	Sequence 1
Investigational medicinal product name	QVM149 150/50/80 µg
Investigational medicinal product code	QVM149
Other name	QVM149
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Hard capsule

Arm title	Sequence 2

Arm description:

Patients received in a sequential order the following interventional treatments: B, A and C.

Arm type	Sequence 2

No investigational medicinal product assigned in this arm

Arm title	Sequence 3

Arm description:

Patients received in a sequential order the following interventional treatments: C, B and A.

Arm type	Sequence 3

No investigational medicinal product assigned in this arm

Arm title	Sequence 4

Arm description:

Patients received in a sequential order the following interventional treatments : C, A and B.

Arm type	Sequence 4

No investigational medicinal product assigned in this arm

Arm title	Sequence 5

Arm description:

Patients received in a sequential order the following interventional treatments: A, C and B.

Arm type	Sequence 5

No investigational medicinal product assigned in this arm

Arm title	Sequence 6

Arm description:

Patients received in a sequential order the following interventional treatments: B, C and A.

Arm type	Sequence 6

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Sequence 1	Sequence 2	Sequence 3
Started	7	6	6
Completed	7	6	6
Not completed	0	0	0
Subject/Guardian Decision	-	-	-

Number of subjects in period 1	Sequence 4	Sequence 5	Sequence 6
Started	6	6	6
Completed	4	6	6
Not completed	2	0	0
Subject/Guardian Decision	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	37	37	
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)	35	35	
From 65-84 years	2	2	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	43.5		
standard deviation	± 14.04	-	
Sex: Female, Male Units: Subjects			
Female	16	16	
Male	21	21	
Race (NIH/OMB) Units: Subjects			
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	

Subject analysis sets	
Subject analysis set title	All participants
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants randomized to one of six treatment sequences

Subject analysis set title	QVM149 am
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients will receive in a sequential order the following interventional treatments A,B and C

Subject analysis set title	QVM149 pm
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: B, A and C.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients will receive in a sequential order the following interventional treatments: C, B and A.	
Subject analysis set title	QVM149 am
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: A,B and C.	
Subject analysis set title	QVM149 pm
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: B, A and C.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: C, B and A.	

Reporting group values	All participants	QVM149 am	QVM149 pm
Number of subjects	37	30	30
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	43.5		
standard deviation	± 14.04	±	±
Sex: Female, Male Units: Subjects			
Female	16		
Male	21		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	35		

More than one race	0		
Unknown or Not Reported	2		

Reporting group values	Placebo	QVM149 am	QVM149 pm
Number of subjects	33	35	35
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			

Reporting group values	Placebo		
Number of subjects	36		
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
Reporting group description:	
Patients received in a sequential order the following interventional treatments: A,B and C.	
Reporting group title	Sequence 2
Reporting group description:	
Patients received in a sequential order the following interventional treatments: B, A and C.	
Reporting group title	Sequence 3
Reporting group description:	
Patients received in a sequential order the following interventional treatments: C, B and A.	
Reporting group title	Sequence 4
Reporting group description:	
Patients received in a sequential order the following interventional treatments : C, A and B.	
Reporting group title	Sequence 5
Reporting group description:	
Patients received in a sequential order the following interventional treatments: A, C and B.	
Reporting group title	Sequence 6
Reporting group description:	
Patients received in a sequential order the following interventional treatments: B, C and A.	
Subject analysis set title	All participants
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants randomized to one of six treatment sequences	
Subject analysis set title	QVM149 am
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients will receive in a sequential order the following interventional treatments A,B and C	
Subject analysis set title	QVM149 pm
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: B, A and C.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients will receive in a sequential order the following interventional treatments: C, B and A.	
Subject analysis set title	QVM149 am
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: A,B and C.	
Subject analysis set title	QVM149 pm
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: B, A and C.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients received in a sequential order the following interventional treatments: C, B and A.	

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

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

End point description:

Weighted mean forced expiratory volume in 1 second (FEV1) over 24 h (AUC0-24h) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo.

End point type	Primary

End point timeframe:

At the end of each treatment period day 14 pre-dose to 24 hours post-dose.

End point values	QVM149 am	QVM149 pm	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	30	33	
Units: Liters				
least squares mean (standard error)	3.4305 (± 0.15242)	3.4361 (± 0.15213)	2.8209 (± 0.15259)	

Statistical analyses

Statistical analysis title	Treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 am v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Linear mixed model
Point estimate	0.6096
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.538
upper limit	0.6811

Statistical analysis title	Treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 pm v Placebo

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	0.6152
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5437
upper limit	0.6868

Statistical analysis title	treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 am v QVM149 pm
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	-0.0057
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.076
upper limit	0.0647

Secondary: Trough FEV1 after 24h

End point title	Trough FEV1 after 24h

End point description:

FEV1 at approximately 24 h after the last p.m. or penultimate a.m. dose. Morning and evening trough FEV1 (L) were analyzed by time of day. For morning trough FEV1 (L) assessments this meant that the spirometric assessment was done approximately 24 h after last morning dose and approximately 12 h after last evening dose.

End point type	Secondary

End point timeframe:

At the end of each treatment period day 14 pre-dose to 24 hours post-dose.

End point values	QVM149 am	QVM149 pm	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35	35	36	
Units: Liters				
least squares mean (standard error)				
Morning trough FEV1	3.3731 (± 0.15037)	3.4871 (± 0.15041)	2.7524 (± 1.15120)	

Statistical analyses

Statistical analysis title	Treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 am v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.6206
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5335
upper limit	0.7077

Notes:

[1] - Treatment difference

Statistical analysis title	Treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 pm v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	0.7347
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6469
upper limit	0.8225

Statistical analysis title	Treatment difference

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 am v QVM149 pm
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	-0.1141
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.197
upper limit	-0.0311

Secondary: Peak expiratory flow (PEF)

End point title	Peak expiratory flow (PEF)

End point description:

Peak expiratory flow (PEF) is the maximum flow generated during a forceful exhalation, starting from full lung inflationDaily morning and evening peak expiratory flow rate from Day 2 to Day14 during the three treatment periods.

End point type	Secondary

End point timeframe:

From treatment period start through study completion (up to 19 weeks).

End point values	QVM149 am	QVM149 pm	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35	35	36	
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 analyses

Statistical analysis title	Morning average PEF

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.

Comparison groups	QVM149 am v Placebo

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Mixed models analysis
Parameter estimate	Linear mixed model
Point estimate	72.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	61.3
upper limit	82.9

Notes:

[2] - Treatment difference

Statistical analysis title	Morning average PEF

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 pm v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	86.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.1
upper limit	97.8

Statistical analysis title	Morning average PEF

Statistical analysis description:

A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Comparison groups	QVM149 am v QVM149 pm
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	-14.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-25.6
upper limit	-4.1

Statistical analysis title	Evening average PEF
Comparison groups	QVM149 am v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	73.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	61.9
upper limit	84.2

Notes:

[3] - A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.'

Statistical analysis title	Evening average PEF
Comparison groups	QVM149 pm v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[4]
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	58.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	47.5
upper limit	69.9

Notes:

[4] - A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.

Statistical analysis title	Evening average PEF
Comparison groups	QVM149 am v QVM149 pm
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[5]
Method	Mixed models analysis
Parameter estimate	A hypothesis test is not planned for thi
Point estimate	14.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.3
upper limit	25.5

Notes:

[5] - A hypothesis test is not planned for this study,
inferences are to be performed by interpreting confidence interval of treatment difference.’

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	QVM149
Reporting group description:	
QVM149 morning dose	
Reporting group title	QVM149
Reporting group description:	
QVM149 evening dose	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	QVM149	QVM149	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (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	QVM149	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 35 (31.43%)	13 / 35 (37.14%)	16 / 36 (44.44%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 35 (14.29%)	3 / 35 (8.57%)	7 / 36 (19.44%)
occurrences (all)	5	3	7
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	1 / 36 (2.78%)
occurrences (all)	1	2	1
Dysphonia			
subjects affected / exposed	2 / 35 (5.71%)	3 / 35 (8.57%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Oropharyngeal pain			
subjects affected / exposed	3 / 35 (8.57%)	4 / 35 (11.43%)	2 / 36 (5.56%)
occurrences (all)	3	4	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 35 (5.71%)	5 / 36 (13.89%)
occurrences (all)	2	2	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported