Clinical trial results:
A randomized, double blind, placebo controlled study to assess the safety, tolerability, pharmacokinetics and efficacy of multiple doses of QBW251 in patients with COPD

Summary

EudraCT number	2014-001530-28
Trial protocol	PL
Global end of trial date	23 January 2017

Results information

Result version number	v1 (current)
This version publication date	03 February 2018
First version publication date	03 February 2018

Trial information

Trial identification

Sponsor protocol code	CQBW251X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02449018
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 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	23 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of a 28-day QBW251 treatment course on small airway function in current and prior smokers with chronic bronchitis and COPD

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	30 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United States: 89
Worldwide total number of subjects	92
EEA total number of subjects	3

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)	47
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients completed a single-blind placebo controlled Run-in period (14 days: Day −14 to Day −1) after confirmation of eligibility, which included visits at Day −14 and at Baseline (Day −1).

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	QBW251

Arm description:

QBW251 (28 day treatment period) and placebo (42 days, run-in and wash-out periods)

Arm type	Experimental
Investigational medicinal product name	CQBW251
Investigational medicinal product code	QBW251
Other name	QBW251
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

25 mg hard gelatin capsule

Investigational medicinal product name	QBW251X
Investigational medicinal product code	QBW251
Other name	QBW251
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg hard gelatin capsule

Arm title	Placebo

Arm description:

Placebo (70 days, run-in, treatment and wash-out periods)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo 0mg

Number of subjects in period 1	QBW251	Placebo
Started	64	28
Completed	52	26
Not completed	12	2
Patient decision	2	-
Adverse event, non-fatal	5	1
Protocol deviation	4	-
Administrative problems	1	-
Abnormal laboratory value	-	1

Baseline characteristics

Reporting groups	
Reporting group title	QBW251
Reporting group description:	
QBW251 (28 day treatment period) and placebo (42 days, run-in and wash-out periods)	
Reporting group title	Placebo
Reporting group description:	
Placebo (70 days, run-in, treatment and wash-out periods)	

Reporting group values	QBW251	Placebo	Total
Number of subjects	64	28	92
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	13	47
From 65-84 years	30	15	45
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	63.6	64.9	
standard deviation	± 6.61	± 7.55	-
Gender, Male/Female Units: Subjects			
Female	31	9	40
Male	33	19	52

End points

End points reporting groups	
Reporting group title	QBW251
Reporting group description:	
QBW251 (28 day treatment period) and placebo (42 days, run-in and wash-out periods)	
Reporting group title	Placebo
Reporting group description:	
Placebo (70 days, run-in, treatment and wash-out periods)	

Primary: Change from Baseline in Lung Clearance Index (LCI)	
End point title	Change from Baseline in Lung Clearance Index (LCI)
End point description:	
Change from baseline to Day 29 in LCI as measured by multiple breath nitrogen washout (MBNW) technique. MBNW is the time taken to wash out nitrogen while breathing 100% oxygen.	
End point type	Primary
End point timeframe:	
Day 29	

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Participants				
arithmetic mean (standard deviation)	-0.03 (± 1.28)	-0.16 (± 1.15)		

Statistical analyses

Statistical analysis title	Absolute change from baseline
Comparison groups	QBW251 v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.24
upper limit	0.79
Variability estimate	Standard deviation
Dispersion value	0.31

Secondary: Change From Baseline in FEV1 pre-bronchodilator

End point title	Change From Baseline in FEV1 pre-bronchodilator

End point description:

Change From Baseline to Day 29 in FEV1 will be measured by spirometer before bronchodilator administration. Forced Expiratory Volume in 1 Second (FEV1) is the amount of air that can be exhaled in 1 second. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	23		
Units: Liters				
arithmetic mean (standard deviation)	0.04 (± 0.24)	-0.02 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FEV1 post-bronchodilator

End point title	Change From Baseline in FEV1 post-bronchodilator

End point description:

Change From Baseline to Day 29 in FEV1 will be measured by spirometer after bronchodilator administration. Forced Expiratory Volume in 1 Second (FEV1) is the amount of air that can be exhaled in 1 second. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	24		
Units: Liters				
arithmetic mean (standard deviation)	0.05 (± 0.21)	-0.02 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FVC pre bronchodilator

End point title	Change From Baseline in FVC pre bronchodilator

End point description:

Change From Baseline to Day 29 in FVC will be measured by spirometer before bronchodilator administration. Forced Vital Capacity (FVC) is the maximum amount of air a person can expel from the lungs after a maximum inhalation. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability. Forced vital capacity (FVC) as a measure of lung function, measured before bronchodilator

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	23		
Units: Liters				
least squares mean (standard deviation)	0.07 (± 0.05)	0.01 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FVC post- bronchodilator

End point title	Change From Baseline in FVC post- bronchodilator

End point description:

Change From Baseline to Day 29 in FVC will be measured by spirometer after bronchodilator administration. Forced Vital Capacity (FVC) is the maximum amount of air a person can expel from the lungs after a maximum inhalation. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability. Forced vital capacity (FVC) as a measure of lung function, measured after bronchodilator

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	24		
Units: Liters				
least squares mean (standard deviation)	0.03 (± 0.04)	0.01 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in TLC

End point title	Change From Baseline in TLC

End point description:

Change From Baseline to Day 29 in TLC will be measured by spirometry. Total lung capacity (TLC) is the volume in the lungs at maximal inflation. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Liters				
least squares mean (standard deviation)	0.01 (± 0.07)	-0.07 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RV

End point title	Change From Baseline in RV

End point description:

Change From Baseline to Day 29 in RV will be measured by spirometry. Residual volume (RV) is the volume of air remaining in the lungs after a maximal exhalation. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	24		
Units: Liters				
least squares mean (standard deviation)	0.03 (± 0.07)	-0.02 (± 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FRC

End point title	Change From Baseline in FRC

End point description:

Change From Baseline to Day 29 in FRC will be measured by spirometry. Functional residual capacity (FRC) is the volume in the lungs at the end-expiratory position. All spirometry calibrations and evaluations will follow the recommendations of the American Thoracic Society / European Respiratory Society guidelines for acceptability.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	24		
Units: Liters				
least squares mean (standard deviation)	0.01 (± 0.07)	-0.02 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DLCO

End point title	Change From Baseline in DLCO

End point description:

Diffusing capacity of the lung for carbon monoxide (DLCO) is the extent to which oxygen passes from the lung to the blood.

End point type	Secondary

End point timeframe:

Day 29

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	22		
Units: ml/min/mmHg				
least squares mean (standard deviation)	-0.91 (± 0.24)	-0.25 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of QBW251 by TMax

End point title	Plasma concentration of QBW251 by TMax[1]

End point description:

Tmax is the time to reach the maximum concentration after drug administration.

End point type	Secondary

End point timeframe:

Day 1, Day 28

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No stats analysis for this outcome measure

End point values	QBW251			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: hr				
median (full range (min-max))				
Day 1 (n=57)|	1.27 (0.983 to 8.03)			
Day 28 (n=53)|	1.98 (0.933 to 7.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of QBW251 by CMax

End point title	Plasma concentration of QBW251 by CMax[2]

End point description:

Cmax is the observed maximum plasma concentration following drug administration.

End point type	Secondary

End point timeframe:

Day 1, Day 28

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No stats analysis for this outcome measure

End point values	QBW251			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=57)| Day 28 (n=53)|	1250 (± 840) 1640 (± 916)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of QBW251 by AUClast

End point title	Plasma concentration of QBW251 by AUClast[3]

End point description:

AUClast is the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration.

End point type	Secondary

End point timeframe:

Day 1, Day 28

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No stats analysis for this outcome measure

End point values	QBW251			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: hr×ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=57)| Day 28 (n=53)|	3830 (± 3280) 6840 (± 4490)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of QBW251 by AUC0-12h

End point title	Plasma concentration of QBW251 by AUC0-12h

End point description:

AUC 0-12h is the area under the plasma concentration-time curve from time zero to 12 hours.

End point type	Secondary

End point timeframe:

Day 1, Day 28

End point values	QBW251	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: hr×ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - analysis AUClast was not calculated up to 12 hours after dosing So this data is not available.

[5] - analysis AUClast was not calculated up to 12 hours after dosing So this data is not available.

Statistical analyses

No statistical analyses for this end point

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	19.1

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	QBW251 300 mg bid
Reporting group description:	
QBW251 300 mg bid	

Serious adverse events	Placebo	QBW251 300 mg bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	4 / 64 (6.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	QBW251 300 mg bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)	6 / 64 (9.38%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 28 (7.14%)	3 / 64 (4.69%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2015	The purpose was to clarify multiple requirements related to the chest HRCT study component. HRCT was utilized as a screening measurement as well as a mechanism to quantify air trapping for comparative efficacy purposes in this study. Experience in ongoing sponsor trials revealed that historical scans are unlikely to adhere to the imaging requirements of this study. Therefore, the use of historical HRCT scans for the purpose of air trapping quantification was removed, except in the instance that a patient was re-screened for this study. The specific quantitative thresholds used to determine evidence of air trapping and emphysema extent was removed from the radiologic eligibility criteria and only a qualitative description remained.
01 July 2015	The purpose was to modify the dose of QBW251, changing from the original dose of 450 mg bid to 300 mg bid. At the time of the protocol amendment, 4 patients were randomized to 450 mg bid (drug/placebo).
01 February 2016	The purpose was to discontinue the collection and analysis of EPCs. EPC cellular biomarkers were collected as an exploratory objective to evaluate vascular remodeling in COPD patients. Results from the analysis of 136 EPC samples from a total of 44 patients showed that blood leukocyte populations and EPCs could not be identified properly because of staining failure and quality issue of the reagents. Based on this data, cellular biomarkers were removed as an exploratory biomarker assessment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported