Clinical trial results:
A randomized, double blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of inhaled QBW276 in patients with cystic fibrosis

Summary

EudraCT number	2014-004915-35
Trial protocol	DE GB
Global end of trial date	04 October 2018

Results information

Result version number	v1 (current)
This version publication date	02 May 2019
First version publication date	02 May 2019

Trial information

Trial identification

Sponsor protocol code	CQBW276X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02566044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis PharmaAG
Sponsor organisation address	CH-4002, Basel, United Kingdom,
Public contact	Medica Information Services, Novartis Pharmaceuticals UK Limited, +44 1276698370, medinfo.uk@novartis.com
Scientific contact	Medica Information Services, Novartis Pharmaceuticals UK Limited, +44 1276698370, medinfo.uk@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	04 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2018
Global end of trial reached?	Yes
Global end of trial date	04 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohorts 1 and 2: To assess the safety, tolerability, and pharmacokinetics (PK) of multiple doses of inhaled QBW276 and its metabolites, over 1 or 2 weeks of treatment in patients with cystic fibrosis regardless of the underlying mutation

Cohort 3: To evaluate the pharmacodynamic (PD) response to multiple doses of inhaled QBW276 in lung function (percent of predicted FEV1) over 4 weeks of treatment compared with placebo in patients with cystic fibrosis that are homozygous for the F508del mutation

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	25 September 2017
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	Germany: 13
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	16
EEA total number of subjects	13

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was terminated after completion of all randomized patients in Cohort 2 due to

strategic issues. All patients completed the study prior to termination.

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	Cohort 1 QBW276

Arm description:

QBW276 3mg bid

Arm type	Experimental
Investigational medicinal product name	QBW276 3mg bid
Investigational medicinal product code	QBW276 3mg bid
Other name	QBW276 3mg bid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1.5 mg strength capsule

Arm title	Cohort 2 QBW276

Arm description:

QBW276 Dose 6 mg bid

Arm type	Experimental
Investigational medicinal product name	QBW276 Dose 6 mg bid
Investigational medicinal product code	QBW276 Dose 6 mg bid
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1.5 mg strength capsule

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo

Number of subjects in period 1	Cohort 1 QBW276	Cohort 2 QBW276	Placebo
Started	6	6	4
Completed	6	6	4

Baseline characteristics

End points

End points reporting groups

Reporting group title	Cohort 1 QBW276
Reporting group description: QBW276 3mg bid	
Reporting group title	Cohort 2 QBW276
Reporting group description: QBW276 Dose 6 mg bid	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Cohort 1 QBP545
Subject analysis set type	Safety analysis
Subject analysis set description: formation of metabolites QBP545	
Subject analysis set title	Cohort 1 QBV697
Subject analysis set type	Safety analysis
Subject analysis set description: formation of metabolites QBV697	
Subject analysis set title	Cohort 2 QBP545
Subject analysis set type	Safety analysis
Subject analysis set description: formation of metabolites QBP545	
Subject analysis set title	Cohort 2 QBV697
Subject analysis set type	Safety analysis
Subject analysis set description: formation of metabolites QBV697	

Primary: Cohorts 1 and 2: Safety Assessments, incidence of Treatment-Emergent Adverse Events

End point title	Cohorts 1 and 2: Safety Assessments, incidence of Treatment-Emergent Adverse Events[1]

End point description:

Adverse events were summarized by the number of patients having any adverse event overall and presented in the safety section. Study was prematurely terminated

End point type	Primary

End point timeframe:

Cohort 1: day 1-7; Cohort 2: day 1-14

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for safety

End point values	Cohort 1 QBW276	Cohort 2 QBW276	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	4	
Units: Participants	6	6	4	

Statistical analyses

No statistical analyses for this end point

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	QBW276 3 mg bid
Reporting group description: QBW276 3 mg bid	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	QBW276 6 mg bid
Reporting group description: QBW276 6 mg bid	

Serious adverse events	QBW276 3 mg bid	Placebo	QBW276 6 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	0 / 6 (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: 2 %

Non-serious adverse events	QBW276 3 mg bid	Placebo	QBW276 6 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	6 / 6 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood creatine phosphokinase			

increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	5
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	4 / 6 (66.67%)
occurrences (all)	0	0	6
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	3
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sputum increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2015	This amendment to the protocol was to make specific changes that address comments received from the UK MHRA on 12 Nov 2015 in response to the Sponsors clinical trial application (CTA) submission. The MHRA stated their comments were grounds for non-acceptance of the CTA and that a protocol amendment was required. The changes made to the protocol included additional detail on the duration for use of contraception after the last dose of QBW276, inclusion of the prohibited medications list within the protocol, amendments to the study stopping rules and some corrections of typographical errors. As this amendment to the protocol has occurred prior to study start, these changes did not affect the study population or study results
01 March 2017	The purpose of this amendment was to revise the Assessment Schedule to comply with Health Authority requirements that all studies must be collected and submitted in CDISC (Clinical Data Interchange Standards Consortium) compliant format. To adhere to these requirements, the protocol was amended to SDTM (Study Data Tabulation Model) format. After completing exploratory biomarker analysis in the QBW251 trials, no significant or relevant signals were detected in the biomarker assays conducted. As a result, other than aldosterone and electrolytes, the exploratory biomarker analysis was removed. In addition, some minor modifications and corrections were made throughout the document to ensure clarity and consistency. As this amendment to the protocol occurred prior to study start, these changes did not affect the study population or study results. This amendment does not affect the safety or physical or mental integrity of the subjects of the study, the scientific value of the study, or the conduct or management of the study.
01 August 2017	The purpose of this amendment was to address the request from Health Authorities to exclude patients with hypersensitivity to excipients. In addition, few minor corrections were made and missing reference for CF Quality of Life Questionnaire was added
01 June 2018	The purpose of this amendment was to remove Lung Volumes and MBNW (Multiple Breath Nitrogen Washout) assessments, and to adjust and clarify the assessment schedule, allowing more time for screening and baseline assessments in Cohort 3. The inclusion and exclusion criteria were also revised. In addition, some minor modifications and corrections were made throughout the document to ensure clarity and consistency

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, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: