Clinical trial results:
A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long term Open-label Period to Investigate Ivacaftor in Subjects With Cystic Fibrosis Aged 3 Through 5 Years Who Have a Specified CFTR Gating Mutation

Summary

EudraCT number	2015-001267-39
Trial protocol	GB FR
Global end of trial date	08 August 2017

Results information

Result version number	v1 (current)
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	VX15-770-123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02742519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2017
Global end of trial reached?	Yes
Global end of trial date	08 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Ivacaftor treatment, measured by lung clearance index (LCI) in subjects with cystic fibrosis (CF) who have a specified CF transmembrane conductance regulator (CFTR) gating mutation, and are 3 through 5 years of age at the start of the study.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2016
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	United Kingdom: 7
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	14
EEA total number of subjects	7

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)	14
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study consisted of 2 parts: Part 1- Double Blind (DB) Crossover Treatment Period and Part 2- Open Label Period.

Period 1

Period 1 title	Part 1: DB Treatment 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: Ivacaftor First, Then Placebo

Arm description:

Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1.

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

Dosage and administration details:

Placebo matched to Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 2.

Arm title	Sequence 2: Placebo First, Then Ivacaftor

Arm description:

Placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 2.

Number of subjects in period 1	Sequence 1: Ivacaftor First, Then Placebo	Sequence 2: Placebo First, Then Ivacaftor
Started	8	6
Completed Treatment Period 1	8	6
Started Treatment Period 2	8	6
Completed	7	5
Not completed	1	1
Availability of commercial drug	1	1

Period 2

Period 2 title	Part 2: Open Label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ivacaftor

Arm description:

Ivacaftor administered every 12 hours in open label period.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor administered every 12 hours in open label period.

Number of subjects in period 2[1]	Ivacaftor
Started	10
Completed	0
Not completed	10
Availability of commercial drug	9
Unspecified	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Out of 12 subjects who completed double blind crossover treatment period, only 10 subjects entered the Open Label period.

Baseline characteristics

Reporting groups

Reporting group title	Sequence 1: Ivacaftor First, Then Placebo

Reporting group description:

Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Reporting group title	Sequence 2: Placebo First, Then Ivacaftor

Reporting group description:

Placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Reporting group values	Sequence 1: Ivacaftor First, Then Placebo	Sequence 2: Placebo First, Then Ivacaftor	Total
Number of subjects	8	6	14
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	3.6	4.2	
standard deviation	± 0.7	± 1.0	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	4	5	9

End points

End points reporting groups

Reporting group title	Sequence 1: Ivacaftor First, Then Placebo

Reporting group description:

Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Reporting group title	Sequence 2: Placebo First, Then Ivacaftor

Reporting group description:

Placebo matched to Ivacaftor administered every 12 hours for 8 weeks in treatment period 1 followed by Ivacaftor administered every 12 hours for 8 weeks in treatment period 2. Washout period of 8 weeks occurred between treatment period 1 and treatment period 2.

Reporting group title	Ivacaftor

Reporting group description:

Ivacaftor administered every 12 hours in open label period.

Subject analysis set title	Placebo (Crossover Part)
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo matched to Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1 or treatment period 2.

Subject analysis set title	Ivacaftor (Crossover Part)
Subject analysis set type	Full analysis

Subject analysis set description:

Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1 or treatment period 2.

Primary: Absolute Change From Baseline in Lung Clearance Index (LCI2.5) Through Week 8

End point title	Absolute Change From Baseline in Lung Clearance Index (LCI2.5) Through Week 8

End point description:

LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. Full Analysis Set (FAS) was used which included all randomised subjects who had mutation on at least 1 allele, received at least 1 dose of study drug (Ivacaftor or placebo) and had at least 1 post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline, Through Week 8

End point values	Placebo (Crossover Part)	Ivacaftor (Crossover Part)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: Lung clearance index				
arithmetic mean (standard deviation)	-0.07 (± 0.93)	-0.53 (± 1.23)		

Statistical analyses

Statistical analysis title	Absolute Change From Baseline in LCI2.5

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 13. "Number of subjects included in analysis = 26" is reflected due to EudraCT database limitation.

Comparison groups	Ivacaftor (Crossover Part) v Placebo (Crossover Part)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2121
Method	paired t-test

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Month 15	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Ivacaftor (Crossover Part)
Reporting group description: Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1 or treatment period 2.	
Reporting group title	Placebo (Crossover Part)
Reporting group description: Placebo matched to Ivacaftor administered orally every 12 hours for 8 weeks in treatment period 1 or treatment period 2.	
Reporting group title	Ivacaftor (Open Label Part)
Reporting group description: Ivacaftor administered orally every 12 hours in open label period.	

Serious adverse events	Ivacaftor (Crossover Part)	Placebo (Crossover Part)	Ivacaftor (Open Label Part)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ivacaftor (Crossover Part)	Placebo (Crossover Part)	Ivacaftor (Open Label Part)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 13 (84.62%)	11 / 13 (84.62%)	6 / 10 (60.00%)
Investigations			
Haemophilus test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Streptococcus test positive			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Bacterial test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pseudomonas test positive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 13 (23.08%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	3 / 13 (23.08%)	3 / 10 (30.00%)
occurrences (all)	1	3	3
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 13 (23.08%)	2 / 13 (15.38%)	4 / 10 (40.00%)
occurrences (all)	3	3	5
Productive cough			
subjects affected / exposed	3 / 13 (23.08%)	3 / 13 (23.08%)	0 / 10 (0.00%)
occurrences (all)	3	3	0
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)	2 / 13 (15.38%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Wheezing			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 13 (23.08%)	3 / 13 (23.08%)	3 / 10 (30.00%)
occurrences (all)	4	3	6
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	3 / 13 (23.08%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Bacterial disease carrier			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 13 (7.69%) 1	0 / 10 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2015	- Clarified text surrounding liver function testing.
27 October 2016	- Extended screening period and clarified subject eligibility following multiple breath washout (MBW) assessment.
12 April 2017	- Decision taken to terminate the study.

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.

Vertex terminated the study early because of enrollment futility.

Notes: