Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB CT or D1152H-CFTR Mutation

Summary

EudraCT number	2017-000457-39
Trial protocol	Outside EU/EEA
Global end of trial date	18 December 2018

Results information

Result version number	v2 (current)
This version publication date	29 February 2020
First version publication date	04 July 2019
Version creation reason	• New data added to full data set Updated for Consistency with CT.gov Results

Trial information

Trial identification

Sponsor protocol code	VX16-770-127

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03068312
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
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	22 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2018
Global end of trial reached?	Yes
Global end of trial date	18 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ivacaftor (IVA) treatment in subjects with cystic fibrosis (CF) 6 years of age and older who have a 3849 + 10KB CT or D1152H CF transmembrane conductance regulator gene (CFTR) mutation.

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	18 July 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	Israel: 38
Worldwide total number of subjects	38
EEA total number of subjects	0

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)	4
Adolescents (12-17 years)	4
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in subjects with CF.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1: First IVA Then Placebo

Arm description:

Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.

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

Dosage and administration details:

Subjects received IVA 150 milligram (mg) every 12 hours.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to IVA every 12 hours.

Arm title	Sequence 2: First Placebo Then IVA

Arm description:

Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.

Arm type	Experimental
Investigational medicinal product name	Placebo (Matched to IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to IVA every 12 hours.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA 150 mg every 12 hours.

Number of subjects in period 1	Sequence 1: First IVA Then Placebo	Sequence 2: First Placebo Then IVA
Started	19	19
Completed	19	19

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1: First IVA Then Placebo
Reporting group description:	
Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.	
Reporting group title	Sequence 2: First Placebo Then IVA
Reporting group description:	
Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.	

Reporting group values	Sequence 1: First IVA Then Placebo	Sequence 2: First Placebo Then IVA	Total
Number of subjects	19	19	38
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	32.6	32.1	
standard deviation	± 15.3	± 15.6	-
Gender categorical			
Units: Subjects			
Female	10	10	20
Male	9	9	18
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	19	19	38
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	19	19	38
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Lung Clearance Index 2.5 (LCI2.5)			
Measure 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.			
Units: Lung clearance index			
arithmetic mean	12.74	13.19	
standard deviation	± 4.04	± 5.45	-

End points

End points reporting groups

Reporting group title	Sequence 1: First IVA Then Placebo
Reporting group description:	
Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.	
Reporting group title	Sequence 2: First Placebo Then IVA
Reporting group description:	
Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received placebo matched to IVA for 8 weeks in treatment period 1 or 2.	
Subject analysis set title	IVA
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received IVA for 8 weeks in treatment period 1 or 2.	

Primary: Change in Lung Clearance Index 2.5

End point title	Change in Lung Clearance Index 2.5
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. The Full Analysis Set (FAS) included all randomized subjects who carried the intended CFTR allele mutation and received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
From baseline through 8 weeks	

End point values	Placebo	IVA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	37		
Units: Lung clearance index				
least squares mean (standard error)	0.20 (± 0.19)	-0.46 (± 0.19)		

Statistical analyses

Statistical analysis title	Placebo vs IVA
Statistical analysis description:	
The "number of subjects included in analysis" was 37 instead of 74 because this study has a cross-over design and same subjects received both the interventions. The number "74" is auto-calculated as the sum of numbers presented in 2 comparison groups and is appearing due to EudraCT database format constraints.	
Comparison groups	Placebo v IVA

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least squares mean difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.21

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to safety follow-up visit (up to Week 28)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
All subjects who received placebo matched to IVA for 8 weeks in treatment period 1 or 2.	
Reporting group title	Ivafactor
Reporting group description:	
All subjects who received IVA for 8 weeks in treatment period 1 or 2.	

Serious adverse events	Placebo	Ivafactor	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 38 (5.26%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 38 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ivafactor	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 38 (50.00%)	12 / 38 (31.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 38 (5.26%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Malaise			
subjects affected / exposed	2 / 38 (5.26%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	2 / 38 (5.26%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 38 (5.26%)	3 / 38 (7.89%)	
occurrences (all)	6	4	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 38 (5.26%)	5 / 38 (13.16%)	
occurrences (all)	2	5	
Upper respiratory tract infection			
subjects affected / exposed	6 / 38 (15.79%)	3 / 38 (7.89%)	
occurrences (all)	6	3	
Viral upper respiratory tract infection			
subjects affected / exposed	9 / 38 (23.68%)	1 / 38 (2.63%)	
occurrences (all)	9	1	

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