Clinical trial results:
A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation

Summary

EudraCT number	2017-001379-21
Trial protocol	GB IE DE
Global end of trial date	02 October 2023

Results information

Result version number	v1
This version publication date	14 April 2024
First version publication date	14 April 2024

Trial information

Trial identification

Sponsor protocol code	VX15-770-126

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03277196
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000335-PIP01-08
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	26 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2023
Global end of trial reached?	Yes
Global end of trial date	02 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of long-term ivacaftor treatment in subjects with CF who are less than (<) 24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	28 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	86
EEA total number of subjects	9

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	86

months)	
Children (2-11 years)	0
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:

This study was planned to include 2 arms: an ivacaftor arm (open-label, 96-week treatment period) and an observational arm. However, there were no subjects enrolled in the observational arm. A total of 86 subjects enrolled in the Ivacaftor arm.

Pre-assignment

Screening details:

The subjects who completed parent study VX15-770-124 (NCT02725567) or who did not participate in VX15-770-124 and who are <24 months of age at the Day 1 were enrolled in this study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IVA treatment

Arm description:

Subjects weighing 5 to less than (<) 7 kilogram (kg) received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h in the treatment period for up to 96 weeks. Doses were determined based on safety and pharmacokinetic (PK) data from parent study, age and weight.

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

Dosage and administration details:

Subjects received IVA dose every 12 hours.

Number of subjects in period 1	IVA treatment
Started	86
Completed	58
Not completed	28
Commercial Drug is Available for Subject	20
Other	2
Lost to follow-up	3
Withdrawal of Consent (not due to AE)	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description:

Baseline data is based on the parent study baseline, which is defined as the most recent non-missing measurement collected before the first dose of study drug in the treatment period of parent study.

Reporting group values	Overall Period	Total	
Number of subjects	86	86	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	 10.2 ± 5.19	 -	
Gender categorical Units: Subjects			
Female	40	40	
Male	46	46	

End points

End points reporting groups

Reporting group title	IVA treatment

Reporting group description:

Subjects weighing 5 to less than (<) 7 kilogram (kg) received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h in the treatment period for up to 96 weeks. Doses were determined based on safety and pharmacokinetic (PK) data from parent study, age and weight.

Primary: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs[1]

End point description:

Safety Set included all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Day 1 up to Week 120

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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	IVA treatment			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: Subjects				
Subjects with TEAEs	85			
Subjects with SAEs	21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 120	
Adverse event reporting additional description:	
Safety Set included all subjects who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	IVA treatment
Reporting group description:	
Subjects weighing 5 to <7kg received 25 mg IVA, 7 to <14 kg received 50 mg IVA, and those weighing 14 to <25 kg received 75 mg IVA q12h in the treatment period for up to 96 weeks. Doses were determined based on safety and PK data from parent study, age and weight.	

Serious adverse events	IVA treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 86 (24.42%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram QT shortened			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Electroencephalogram abnormal			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonas test positive			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 86 (2.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital cellulitis			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral rash			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IVA treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 86 (96.51%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 86 (8.14%)		
occurrences (all)	12		
Pseudomonas test positive			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	12		
Haemophilus test positive			
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	11		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	6 / 86 (6.98%) 9		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 34 / 86 (39.53%) 62		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 6 / 86 (6.98%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 15 / 86 (17.44%) 20 7 / 86 (8.14%) 7 22 / 86 (25.58%) 38 13 / 86 (15.12%) 14		
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 33 / 86 (38.37%) 71 13 / 86 (15.12%) 15 60 / 86 (69.77%) 155		
Skin and subcutaneous tissue disorders Dermatitis diaper			

subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	21 / 86 (24.42%)		
occurrences (all)	24		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	10		
Influenza			
subjects affected / exposed	8 / 86 (9.30%)		
occurrences (all)	8		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	13 / 86 (15.12%)		
occurrences (all)	27		
Gastroenteritis			
subjects affected / exposed	9 / 86 (10.47%)		
occurrences (all)	12		
Ear infection			
subjects affected / exposed	19 / 86 (22.09%)		
occurrences (all)	39		
Nasopharyngitis			
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	15		
Otitis media			
subjects affected / exposed	10 / 86 (11.63%)		
occurrences (all)	14		
Respiratory tract infection viral			
subjects affected / exposed	5 / 86 (5.81%)		
occurrences (all)	7		
Rhinitis			
subjects affected / exposed	11 / 86 (12.79%)		
occurrences (all)	21		
Viral upper respiratory tract infection			

subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	11		
Upper respiratory tract infection			
subjects affected / exposed	24 / 86 (27.91%)		
occurrences (all)	39		
Tonsillitis			
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	6 / 86 (6.98%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2017	Amended to remove study visit at Week 104, as the 2 year treatment period concludes at Week 96; For subjects not from Study 124 Part B, revised inclusion criterion to change lower weight bound at screening to comply with request from Regulatory Health Authority. Revised study population and inclusion criteria to include subjects with CF <24 months of age who have an ivacaftor responsive CFTR mutation on at least 1 allele.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported