Clinical trial results:
A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2019-003112-31
Trial protocol	Outside EU/EEA
Global end of trial date	17 July 2019

Results information

Result version number	v1
This version publication date	01 February 2020
First version publication date	01 February 2020

Trial information

Trial identification

Sponsor protocol code	VX16-809-116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03125395
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-001582-PIP01-13
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	20 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2019
Global end of trial reached?	Yes
Global end of trial date	17 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of lumacaftor (LUM)/ivacaftor (IVA) combination therapy in subjects aged 2 years and older with cystic fibrosis (CF), homozygous for F508del.

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	12 May 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	United States: 50
Country: Number of subjects enrolled	Canada: 7
Worldwide total number of subjects	57
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)	57
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:

This study was conducted in subjects with cystic fibrosis (CF) aged 2 years and older.

Period 1

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

Arms

Arm title	LUM/IVA

Arm description:

Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks.
Subjects <6 years of age and weighing >=14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/VX-770
Other name	Lumacaftor/Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects who received LUM/IVA every 12 hours.

Number of subjects in period 1	LUM/IVA
Started	57
Completed	47
Not completed	10
Commercial Drug is Available for Subject	5
Adverse Event	2
Physician Decision	2
Withdrawal of Consent (Not Due to AE)	1

Baseline characteristics

Reporting groups	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks. Subjects <6 years of age and weighing >=14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.	

Reporting group values	LUM/IVA	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	 43.2 ± 12.17	 -	
Gender categorical Units: Subjects			
Female	28	28	
Male	29	29	

End points

End points reporting groups

Reporting group title	LUM/IVA

Reporting group description:

Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks.
Subjects <6 years of age and weighing >=14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

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

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

End point description:

End point type	Primary

End point timeframe:

Up to 98 weeks

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 primary safety endpoint.

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: subjects				
AEs	56			
SAEs	15			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 98 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	LUM/IVA

Reporting group description:

Subjects <6 years of age and weighing <14 kg at enrollment received LUM 100 mg/IVA 125 mg for 96 weeks. Subjects <6 years of age and weighing >=14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

Serious adverse events	LUM/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 57 (26.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematemesis			

subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Sleep apnoea syndrome				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis viral				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis adenovirus				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 57 (1.75%)			
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	6 / 57 (10.53%)		
occurrences causally related to treatment / all	3 / 9		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	1 / 57 (1.75%)		
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	LUM/IVA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 57 (96.49%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	19		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	8		
Forced expiratory volume decreased			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased			

subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Pseudomonas test positive			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	9		
Staphylococcus test positive			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	14		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	23 / 57 (40.35%)		
occurrences (all)	42		
Vessel puncture site pain			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	14		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Vomiting			

subjects affected / exposed	17 / 57 (29.82%)		
occurrences (all)	22		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	47 / 57 (82.46%)		
occurrences (all)	159		
Dyspnoea			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Lower respiratory tract congestion			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	37		
Nasal discharge discolouration			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	12		
Productive cough			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	8		
Rhinorrhoea			
subjects affected / exposed	18 / 57 (31.58%)		
occurrences (all)	26		
Sinus congestion			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Sputum increased			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	8		
Upper respiratory tract congestion			

subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	5		
Wheezing			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Ear infection			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	21		
Hand-foot-and-mouth disease			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	17		
Influenza			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	20		
Otitis media			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	9		
Pharyngitis streptococcal			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	11		
Pneumonia			

subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	17		
Upper respiratory tract infection			
subjects affected / exposed	13 / 57 (22.81%)		
occurrences (all)	16		
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		

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