Clinical trial results:
A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for F508del and 12 to <24 Months of Age at Treatment Initiation

Summary

EudraCT number	2023-000946-41
Trial protocol	Outside EU/EEA
Global end of trial date	22 August 2023

Results information

Result version number	v2 (current)
This version publication date	06 October 2024
First version publication date	06 March 2024
Version creation reason	• New data added to full data set Secondary end points added.

Trial information

Trial identification

Sponsor protocol code	VX19-809-124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04235140
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	18 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2023
Global end of trial reached?	Yes
Global end of trial date	22 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of long-term lumacaftor/ivacaftor (LUM/IVA) treatment in subjects with cystic fibrosis (CF), who are homozygous for F508del and 12 to less than (<) 24 months of age at treatment initiation.

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	24 February 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Canada: 13
Worldwide total number of subjects	52
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)	52
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: -

Pre-assignment

Screening details:

This study was conducted in subjects with CF aged 12 months through less than 24 months of age at treatment initiation who were homozygous for F508del and subjects who completed the 24-week treatment period along with the safety follow-up in study VX16-809-122 (NCT03601637) Part B.

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 weighing 7 to less than (<) 9 kilograms (kg) received LUM 75 milligrams (mg)/IVA 94 mg fixed-dose combination (FDC) every 12 hours (q12h) and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h of 96 weeks. Subjects weighing greater than or equal to (>=)14 kg received LUM 150 mg/IVA 188 mg FDC q12h of 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 received LUM/IVA FDC every 12 hours.

Number of subjects in period 1	LUM/IVA
Started	52
Rollover Subjects	39
LUM/IVA-Naïve Subjects	13 [1]
Completed	38
Not completed	14
Adverse Event	2
Lost to follow-up	1
Withdrawal of consent (not due to AE)	4
Commercial drug is available for subject	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A total of 52 subjects were enrolled in the study. However, only 39 subjects rolled over from the VX16-809-122 study to this study, and the rest who enrolled were LUM-IVA naive. Subjects in LUMN-IVA naive group are those who did not participated in Study VX16-809-122.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period
Reporting group description:	
Baseline value was defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose of LUM/IVA in Study 124.	

Reporting group values	Overall Period	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	18.8		
standard deviation	± 3.32	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	28	28	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	43	43	
Not Collected per Local Regulations	8	8	
Race Units: Subjects			
White	40	40	
Black or African American	0	0	
Asian	0	0	
American Indian or Alaska Native	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Not collected per local regulations	8	8	
Other	1	1	
More than one race	2	2	

End points

End points reporting groups

Reporting group title	LUM/IVA

Reporting group description:

Subjects weighing 7 to less than (<) 9 kilograms (kg) received LUM 75 milligrams (mg)/IVA 94 mg fixed-dose combination (FDC) every 12 hours (q12h) and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h of 96 weeks. Subjects weighing greater than or equal to (>=)14 kg received LUM 150 mg/IVA 188 mg FDC q12h of 96 weeks.

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

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

End point description:

Safety set included all subjects who are exposed to any amount of study drug in this study.

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	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: Subjects				
Subjects with TEAEs	52			
Subjects with SAEs	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride (SwCl)

End point title	Absolute Change in Sweat Chloride (SwCl)

End point description:

The Full Analysis Set (FAS) included all subjects who were enrolled and dosed in this study. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

End point type	Secondary

End point timeframe:

From Baseline at Week 96

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)	-21.0 (± 14.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to Week 120	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	LUM/IVA

Reporting group description:

Subjects weighing 7 to < 9 kg at Day 1 received LUM 75 mg/IVA 94 mg FDC q12h and those weighing 9 to <14 kg at Day 1 received LUM 100 mg/IVA 125 mg q12h of 96 weeks. Subjects weighing >=14 kg at Day 1 received LUM 150 mg/IVA 188 mg FDC q12h of 96 weeks.

Serious adverse events	LUM/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 52 (23.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Near drowning			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	2 / 52 (3.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Distal intestinal obstruction syndrome				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis atopic				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
COVID-19				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis orbital				
subjects affected / exposed	1 / 52 (1.92%)			
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 / 52 (11.54%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection viral				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Parainfluenzae virus infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 52 (1.92%)		
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	50 / 52 (96.15%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Pseudomonas test positive			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
SARS-CoV-2 test positive			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
General disorders and administration			

site conditions Pyrexia subjects affected / exposed occurrences (all)	15 / 52 (28.85%) 24		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 3 / 52 (5.77%) 3 14 / 52 (26.92%) 20 6 / 52 (11.54%) 7 14 / 52 (26.92%) 23		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 25 / 52 (48.08%) 67 9 / 52 (17.31%) 10 15 / 52 (28.85%) 31		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 6 / 52 (11.54%) 6		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) COVID-19	 4 / 52 (7.69%) 4		

subjects affected / exposed	12 / 52 (23.08%)			
occurrences (all)	13			
Conjunctivitis				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	5			
Ear infection				
subjects affected / exposed	12 / 52 (23.08%)			
occurrences (all)	18			
Croup infectious				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Gastroenteritis				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Infective pulmonary exacerbation of cystic fibrosis				
subjects affected / exposed	14 / 52 (26.92%)			
occurrences (all)	32			
Molluscum contagiosum				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Otitis media				
subjects affected / exposed	5 / 52 (9.62%)			
occurrences (all)	6			
Nasopharyngitis				
subjects affected / exposed	3 / 52 (5.77%)			
occurrences (all)	3			
Otitis media acute				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	9			
Respiratory syncytial virus infection				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			
Sinusitis				
subjects affected / exposed	4 / 52 (7.69%)			
occurrences (all)	4			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	16 / 52 (30.77%) 34		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2021	Amended to add the new dose of LUM 75 mg/IVA 94 mg and adjusted the lower weight bound for the LUM 100 mg/IVA 125 mg dose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported