Clinical trial results:
A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del

Summary

EudraCT number	2017-004794-13
Trial protocol	Outside EU/EEA
Global end of trial date	29 October 2021

Results information

Result version number	v1
This version publication date	14 May 2022
First version publication date	14 May 2022

Trial information

Trial identification

Sponsor protocol code	VX16-809-122

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03601637
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	19 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2021
Global end of trial reached?	Yes
Global end of trial date	29 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and pharmacokinetics (PK) of lumacaftor (LUM) and ivacaftor (IVA) in subjects 1 to less than (<) 2 years of age with cystic fibrosis (CF), homozygous for F508del (F/F).

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	23 August 2018
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: 49
Country: Number of subjects enrolled	Canada: 12
Worldwide total number of subjects	61
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)	61
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 1 through less than 2 years of age who are homozygous for F508del.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: LUM/IVA

Arm description:

Subjects received LUM/IVA based on their weight at screening for 15 days.

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 fixed-dose combination (FDC) every 12 hours.

Arm title	Part B: LUM/IVA

Arm description:

Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.

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[1]	Part A: LUM/IVA	Part B: LUM/IVA
Started	14	46
Completed	13	43
Not completed	1	3
Adverse Event	1	1

Other	-	1
Withdrawal of Consent (not due to AE)	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 61 subjects were enrolled in Parts A and B of the study. One subject in Part B was enrolled but not dosed in this study. Therefore data for 60 subjects are reported in the subject disposition and baseline characteristics sections.

Baseline characteristics

Reporting groups	
Reporting group title	Part A: LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 15 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.	

Reporting group values	Part A: LUM/IVA	Part B: LUM/IVA	Total
Number of subjects	14	46	60
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	17.2	18.1	
standard deviation	± 3.6	± 3.5	-
Gender categorical			
Units: Subjects			
Female	7	24	31
Male	7	22	29

End points

End points reporting groups

Reporting group title	Part A: LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 15 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.	
Subject analysis set title	Part A: LUM/IVA - Dose 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received LUM/IVA Dose 1 every 12 hours for 15 days.	
Subject analysis set title	Part A: LUM/IVA - Dose 2
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received LUM/IVA Dose 2 every 12 hours for 15 days.	

Primary: Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA

End point title	Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA[1]
End point description:	
PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Primary
End point timeframe:	
Day 1 and Day 15	

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	Part A: LUM/IVA - Dose 1	Part A: LUM/IVA - Dose 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1: LUM (n=7,7)	14600 (± 5560)	12600 (± 7190)		
Day 15: LUM (n=7,5)	16600 (± 9590)	13900 (± 5800)		
Day 1: IVA (n=7,7)	1620 (± 648)	1320 (± 804)		
Day 15: IVA (n=7,5)	718 (± 352)	496 (± 268)		

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA

End point title	Part A: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA[2]

End point description:

PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.

End point type	Primary

End point timeframe:

Pre-dose at Day 8 and Day 15.

Notes:

[2] - 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	Part A: LUM/IVA - Dose 1	Part A: LUM/IVA - Dose 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 8: LUM (n=7,6)	12000 (± 8880)	12800 (± 3900)		
Day 15: LUM (n=5,6)	8380 (± 7790)	10500 (± 3070)		
Day 8: IVA (n=7,6)	169 (± 75.5)	185 (± 101)		
Day 15: IVA (n=5,6)	78.9 (± 19.1)	120 (± 60.5)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[3][4]

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

End point type	Primary

End point timeframe:

From Day 1 up to Week 26

Notes:

[3] - 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.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint is only applicable for Part B.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subjects				
Subjects with TEAEs	44			
Subjects with SAEs	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 Through Safety Follow-up Period (up to Day 25 for Part A and up to Week 26 for Part B)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Part A : LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 15 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description:	
Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.	

Serious adverse events	Part A : LUM/IVA	Part B: LUM/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural fever			
subjects affected / exposed	0 / 14 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 14 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	0 / 14 (0.00%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A : LUM/IVA	Part B: LUM/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	42 / 46 (91.30%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	4 / 46 (8.70%)	
occurrences (all)	0	4	
Pseudomonas test positive			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Lip injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	1 / 14 (7.14%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	10 / 46 (21.74%)	
occurrences (all)	1	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	5 / 46 (10.87%)	
occurrences (all)	1	7	
Diarrhoea			

subjects affected / exposed	0 / 14 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	8 / 46 (17.39%)	
occurrences (all)	0	9	
Flatulence			
subjects affected / exposed	1 / 14 (7.14%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 14 (28.57%)	16 / 46 (34.78%)	
occurrences (all)	4	27	
Nasal congestion			
subjects affected / exposed	1 / 14 (7.14%)	4 / 46 (8.70%)	
occurrences (all)	1	6	
Rhinorrhoea			
subjects affected / exposed	5 / 14 (35.71%)	5 / 46 (10.87%)	
occurrences (all)	5	9	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 14 (21.43%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
occurrences (all)	0	5	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 14 (0.00%)	8 / 46 (17.39%)	
occurrences (all)	0	12	
Influenza			
subjects affected / exposed	2 / 14 (14.29%)	0 / 46 (0.00%)	
occurrences (all)	2	0	

Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	4 / 46 (8.70%)	
occurrences (all)	0	4	
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	6 / 46 (13.04%)	
occurrences (all)	1	9	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
occurrences (all)	0	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	1 / 46 (2.17%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2019	Amended to update the planned dosing regimen to add lower dose of LUM/IVA in Parts A and B and, to adjust the weight bound of LUM/IVA in Part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported