Clinical trial results:
A Phase 1, Randomized, Open-label Study to Evaluate the Relative Bioavailability, Food Effect, and Dose Proportionality of a Granule Formulation of Lumacaftor in Combination With Ivacaftor in Healthy Adult Subjects

Summary

EudraCT number	2019-002254-23
Trial protocol	Outside EU/EEA
Global end of trial date	01 December 2015

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	VX15-809-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2015
Global end of trial reached?	Yes
Global end of trial date	01 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the relative bioavailability of the granule formulation compared to the tablet formulation of lumacaftor (LUM)/ivacaftor (IVA)

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	22 September 2015
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	United States: 16
Worldwide total number of subjects	16
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 16 subjects were enrolled and randomized in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1

Arm description:

Subjects received LUM/IVA Dose 1 tablet formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 2 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.

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

Dosage and administration details:

Subjects received a single dose of LUM/IVA tablet or granule formulation in the fed or fasted state on Day 1 in treatment period 1, 2, 3 and 4 as per the sequence.

Arm title	Sequence 2

Arm description:

Subjects received LUM/IVA Dose 1 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 2, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.

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

Dosage and administration details:

Subjects received a single dose of LUM/IVA tablet or granule formulation in the fed or fasted state on Day 1 in treatment period 1, 2, 3 and 4 as per the sequence.

Arm title	Sequence 3

Arm description:

Subjects received LUM/IVA Dose 2 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 3, and then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.

Arm type	Experimental

Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/ VX-770
Other name	Lumacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of LUM/IVA tablet or granule formulation in the fed or fasted state on Day 1 in treatment period 1, 2, 3 and 4 as per the sequence.

Arm title	Sequence 4

Arm description:

Subjects received LUM/IVA Dose 1 granule formulation in fasted state in treatment period 1, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.

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

Dosage and administration details:

Subjects received a single dose of LUM/IVA tablet or granule formulation in the fed or fasted state on Day 1 in treatment period 1, 2, 3 and 4 as per the sequence.

Number of subjects in period 1	Sequence 1	Sequence 2	Sequence 3
Started	4	4	4
Completed	4	4	4

Number of subjects in period 1	Sequence 4
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1
Reporting group description:	
Subjects received LUM/IVA Dose 1 tablet formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 2 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 2
Reporting group description:	
Subjects received LUM/IVA Dose 1 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 2, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 3
Reporting group description:	
Subjects received LUM/IVA Dose 2 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 3, and then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 4
Reporting group description:	
Subjects received LUM/IVA Dose 1 granule formulation in fasted state in treatment period 1, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	

Reporting group values	Sequence 1	Sequence 2	Sequence 3
Number of subjects	4	4	4
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	30.8	36.0	37.0
standard deviation	± 4.72	± 9.87	± 11.17
Gender categorical Units: Subjects			
Female	2	2	3
Male	2	2	1

Reporting group values	Sequence 4	Total	
Number of subjects	4	16	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	34.0		
standard deviation	± 16.21	-	

Gender categorical Units: Subjects			
Female	3	10	
Male	1	6	

End points

End points reporting groups

Reporting group title	Sequence 1
Reporting group description:	
Subjects received LUM/IVA Dose 1 tablet formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 2 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 2
Reporting group description:	
Subjects received LUM/IVA Dose 1 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 2, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 3
Reporting group description:	
Subjects received LUM/IVA Dose 2 granule formulation in fed state in treatment period 1, then LUM/IVA Dose 1 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 granule formulation in fasted state in treatment period 3, and then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Reporting group title	Sequence 4
Reporting group description:	
Subjects received LUM/IVA Dose 1 granule formulation in fasted state in treatment period 1, then LUM/IVA Dose 2 granule formulation in fed state in treatment period 2, then LUM/IVA Dose 1 tablet formulation in fed state in treatment period 3, and then LUM/IVA Dose 1 granule formulation in fed state in treatment period 4. A washout period of at least 10 days occurred between each dosing occasion.	
Subject analysis set title	Treatment A: LUM/IVA Dose 1 Tablet (Fed)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received LUM/IVA Dose 1 tablet formulation in fed state.	
Subject analysis set title	Treatment B: LUM/IVA Dose 1 Granule (Fasted)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Subjects who received LUM/IVA Dose 1 granule formulation in fasted state.	
Subject analysis set title	Treatment B: LUM/IVA Dose 1 Granule (Fed)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Subjects who received LUM/IVA Dose 1 granule formulation in fed state.	
Subject analysis set title	Treatment C: LUM/IVA Dose 2 Granule (Fed)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Subjects who received LUM/IVA Dose 2 granule formulation in fed state.	

Primary: Maximum Observed Plasma Concentration (Cmax) of LUM and IVA

End point title	Maximum Observed Plasma Concentration (Cmax) of LUM and IVA[1]
End point description:	
End point type	Primary
End point timeframe:	
Day 1 up to Day 6 for each treatment period	

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 the primary pharmacokinetic (PK) endpoint. PK set included participants who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "Number Analyzed" signifies those participants who
were evaluable for this outcome measure in the specified treatment period.

End point values	Treatment A: LUM/IVA Dose 1 Tablet (Fed)	Treatment B: LUM/IVA Dose 1 Granule (Fasted)	Treatment B: LUM/IVA Dose 1 Granule (Fed)	Treatment C: LUM/IVA Dose 2 Granule (Fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	15	16	15
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
LUM	5590 (± 1150)	3060 (± 1020)	4460 (± 541)	7010 (± 1370)
IVA	643 (± 201)	301 (± 142)	531 (± 111)	837 (± 178)

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve From the Time of Dosing Extrapolated to Infinity [AUC(0 - inf)] of LUM and IVA

End point title	Area Under the Concentration Versus Time Curve From the Time of Dosing Extrapolated to Infinity [AUC(0 - inf)] of LUM and IVA[2]

End point description:

End point type	Primary

End point timeframe:

Day 1 up to Day 6 for each treatment period

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 the primary PK endpoint. PK set included participants who received at least 1 dose of study drug and for whom the primary PK data
were considered to be sufficient and interpretable. Here "Number Analyzed" signifies those participants who
were evaluable for this outcome measure in the specified treatment period.

End point values	Treatment A: LUM/IVA Dose 1 Tablet (Fed)	Treatment B: LUM/IVA Dose 1 Granule (Fasted)	Treatment B: LUM/IVA Dose 1 Granule (Fed)	Treatment C: LUM/IVA Dose 2 Granule (Fed)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	15	16	15
Units: Hours*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)				
LUM	133000 (± 35100)	105000 (± 24600)	118000 (± 22400)	184000 (± 38800)

IVA	7400 (± 2590)	4070 (± 1560)	7160 (± 1880)	11100 (± 2840)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to 10 days after last dose of study drug in treatment period 4	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Treatment A: LUM/IVA Dose 1 Tablet (Fed)
Reporting group description:	
All subjects who received LUM/IVA Dose 1 tablet formulation in fed state.	
Reporting group title	Treatment B: LUM/IVA Dose 1 Granule (Fasted)
Reporting group description:	
All Subjects who received LUM/IVA Dose 1 granule formulation in fasted state.	
Reporting group title	Treatment B: LUM/IVA Dose 1 Granule (Fed)
Reporting group description:	
All Subjects who received LUM/IVA Dose 1 granule formulation in fed state.	
Reporting group title	Treatment C: LUM/IVA Dose 2 Granule (Fed)
Reporting group description:	
All Subjects who received LUM/IVA Dose 2 granule formulation in fed state.	

Serious adverse events	Treatment A: LUM/IVA Dose 1 Tablet (Fed)	Treatment B: LUM/IVA Dose 1 Granule (Fasted)	Treatment B: LUM/IVA Dose 1 Granule (Fed)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment C: LUM/IVA Dose 2 Granule (Fed)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment A: LUM/IVA Dose 1 Tablet (Fed)	Treatment B: LUM/IVA Dose 1 Granule (Fasted)	Treatment B: LUM/IVA Dose 1 Granule (Fed)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)	2 / 15 (13.33%)	3 / 16 (18.75%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 16 (18.75%)	2 / 15 (13.33%)	1 / 16 (6.25%)
occurrences (all)	3	2	1
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	2 / 16 (12.50%)
occurrences (all)	1	1	2
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Eczema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Treatment C: LUM/IVA Dose 2 Granule (Fed)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Eczema subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2 0 / 15 (0.00%) 0		
Infections and infestations Folliculitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		

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