

**Clinical trial results:****A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation****Summary**

EudraCT number	2016-001585-29
Trial protocol	NL
Global end of trial date	04 October 2017

**Results information**

Result version number	v1 (current)
This version publication date	17 May 2018
First version publication date	17 May 2018

**Trial information****Trial identification**

Sponsor protocol code	VX15-809-111
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03061331
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 022101862
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)	No
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	23 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2017
Global end of trial reached?	Yes
Global end of trial date	04 October 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of LUM/IVA in subjects with Cystic Fibrosis (CF) 12 years of age and older who have at least one A455E mutation.

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	31 January 2017
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	Netherlands: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	2
Adults (18-64 years)	18
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 20 subjects were enrolled in this cross-over study.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sequence 1: First LUM/IVA, Then Placebo

Arm description:

Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809/VX-770
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered every 12 hours for 8 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered every 12 hours for 8 weeks.

<b>Arm title</b>	Sequence 2: First Placebo, Then LUM/IVA
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Arm description:

Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809/VX-770
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered every 12 hours for 8 weeks.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered every 12 hours for 8 weeks.

<b>Number of subjects in period 1</b>	Sequence 1: First LUM/IVA, Then Placebo	Sequence 2: First Placebo, Then LUM/IVA
Started	10	10
Completed	8	9
Not completed	2	1
Adverse event	2	1

## Baseline characteristics

### Reporting groups

Reporting group title	Sequence 1: First LUM/IVA, Then Placebo
Reporting group description: Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.	
Reporting group title	Sequence 2: First Placebo, Then LUM/IVA
Reporting group description: Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.	

Reporting group values	Sequence 1: First LUM/IVA, Then Placebo	Sequence 2: First Placebo, Then LUM/IVA	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	41.2 ± 15.1	34.7 ± 11.8	-
Gender categorical Units: Subjects			
Female	7	5	12
Male	3	5	8

## End points

### End points reporting groups

Reporting group title	Sequence 1: First LUM/IVA, Then Placebo
Reporting group description:	Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.
Reporting group title	Sequence 2: First Placebo, Then LUM/IVA
Reporting group description:	Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	Placebo matched to LUM/IVA every 12 hours for 8 weeks in Treatment Period 1 or 2.
Subject analysis set title	LUM/IVA
Subject analysis set type	Full analysis
Subject analysis set description:	LUM/IVA fixed-dose combination every 12 hours for 8 weeks in Treatment Period 1 or 2.

### Primary: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8

End point title	Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8
End point description:	FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.
End point type	Primary
End point timeframe:	Study Baseline, Through Week 8

End point values	Placebo	LUM/IVA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: percentage points				
least squares mean (confidence interval 95%)	2.6 (0.2 to 4.9)	2.7 (0.3 to 5.0)		

### Statistical analyses

Statistical analysis title	Absolute Change From Study Baseline in ppFEV1
Statistical analysis description:	As this is a cross-over study, actual number of subjects analysed for the statistical comparison were 20 (16 of them being counted twice in two treatment periods). "Number of subjects included in analysis = 36 " is incorrect and is reflected due to EudraCT database limitation.
Comparison groups	LUM/IVA v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9277
Method	Mixed Model Repeated Measure (MMRM)
Parameter estimate	Least Squares Mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.7

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 28

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	LUM/IVA
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Reporting group description: -

<b>Serious adverse events</b>	Placebo	LUM/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Placebo	LUM/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	15 / 19 (78.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 18 (11.11%)	3 / 19 (15.79%)	
occurrences (all)	2	3	
Exercise tolerance decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Influenza like illness subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Reproductive system and breast disorders			
Menopausal symptoms subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Menstruation irregular subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Respiratory, thoracic and mediastinal disorders			
Sputum increased subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	3 / 19 (15.79%) 3	
Asthma subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 19 (10.53%) 2	
Cough subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	2 / 19 (10.53%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	2 / 19 (10.53%) 3	
Dysphonia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Paranasal sinus discomfort subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 19 (5.26%) 1	
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Haemoptysis			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	0 / 19 (0.00%) 0	
Respiration abnormal subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Sputum discoloured subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Wheezing subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Psychiatric disorders Libido decreased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Investigations Blood pressure increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Muscle strain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	4 / 19 (21.05%) 4	
Dizziness subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 19 (10.53%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 2	

Paraesthesia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	8 / 19 (42.11%) 8	
Flatulence subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	4 / 19 (21.05%) 4	
Nausea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	4 / 19 (21.05%) 4	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	2 / 19 (10.53%) 2	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 19 (10.53%) 2	
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 19 (5.26%) 1	
Eructation subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Rash pruritic			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Skin exfoliation subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Acne subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Photosensitivity reaction subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 19 (10.53%) 2	
Back pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1	
Arthralgia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	3 / 19 (15.79%) 3	
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	3 / 19 (15.79%) 3	
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	2 / 18 (11.11%)	2 / 19 (10.53%)
occurrences (all)	2	2
Herpes zoster		
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Laryngitis		
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Upper respiratory tract infection		
subjects affected / exposed	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	1
Eye infection		
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	1	0
Impetigo		
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	2	0
Sinusitis		
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	1	0
Tooth infection		
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	1	0
Wound infection		
subjects affected / exposed	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	1	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2017	- Removed restriction on number of subjects with F508del mutation

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported