Clinical trial results:
A Phase 3, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2015-000543-16
Trial protocol	GB DE SE DK BE FR
Global end of trial date	20 September 2016

Results information

Result version number	v1 (current)
This version publication date	19 April 2017
First version publication date	19 April 2017

Trial information

Trial identification

Sponsor protocol code	VX14-809-109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02514473
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)	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	11 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2016
Global end of trial reached?	Yes
Global end of trial date	20 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lumacaftor (LUM) in combination with ivacaftor (IVA) in subjects aged 6 through 11 years with cystic fibrosis (CF), homozygous for the F508del CF transmembrane conductance regulator (CFTR) 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	23 July 2015
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: 103
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Australia: 28
Worldwide total number of subjects	206
EEA total number of subjects	58

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)	206
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:

A total of 206 subjects were randomized in the study, of which 204 subjects were exposed to study treatment (101 subjects received 'Placebo' and 103 subjects received 'LUM/IVA').

Period 1

Period 1 title	Overall (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
Arm title	Placebo

Arm description:

Subjects received placebo matched to lumacaftor (LUM, VX-809) in combination with ivacaftor (IVA, VX-770) fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to LUM in combination with IVA FDC tablet q12h for 24 weeks.

Arm title	LUM/IVA

Arm description:

Subjects received LUM 200 milligram (mg) in combination with IVA 250 mg FDC tablet orally q12h for 24 weeks.

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

Dosage and administration details:

LUM 200 mg in combination with IVA 250 mg tablet orally q12h for 24 weeks.

Number of subjects in period 1[1]	Placebo	LUM/IVA
Started	101	103
Completed	98	98
Not completed	3	5
Consent withdrawn by subject	2	1
Adverse event	-	2
Unspecified	1	1
Lost to follow-up	-	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 206 subjects were randomized in the study, of which 204 subjects were exposed to study drug (101 subjects received 'Placebo' and 103 subjects received 'LUM/IVA'). Subject Disposition and Baseline Characteristics are presented for the 204 subjects who received the study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to lumacaftor (LUM, VX-809) in combination with ivacaftor (IVA, VX-770) fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks.	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects received LUM 200 milligram (mg) in combination with IVA 250 mg FDC tablet orally q12h for 24 weeks.	

Reporting group values	Placebo	LUM/IVA	Total
Number of subjects	101	103	204
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 8.9 ± 1.59	 8.7 ± 1.6	 -
Gender categorical Units: Subjects			
Female	58	63	121
Male	43	40	83

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to lumacaftor (LUM, VX-809) in combination with ivacaftor (IVA, VX-770) fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks.	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects received LUM 200 milligram (mg) in combination with IVA 250 mg FDC tablet orally q12h for 24 weeks.	

Primary: Absolute Change From Baseline in Lung Clearance Index 2.5 (LCI2.5) Through Week 24

End point title	Absolute Change From Baseline in Lung Clearance Index 2.5 (LCI2.5) Through Week 24
End point description:	
Lung clearance index (LCI) is a measure of ventilation inhomogeneity that is derived from a multiple breath washout test using Nitrogen (N2). LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. Analysis was performed on the Full Analysis Set (FAS), which included all randomized subjects who received any amount of study drug. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline through Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	99		
Units: Ratio				
least squares mean (standard error)	0.08 (± 0.13)	-1.01 (± 0.13)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using mixed-effects model for repeated measures (MMRM). The model included treatment, visit and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (less than [<] 25 kilogram [kg] versus greater than or equal to [>=] 25 kg) and percent predicted forced expiratory volume in 1 second (FEV1) severity (<90 versus >=90) at screening.	
Comparison groups	LUM/IVA v Placebo

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	-0.75

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to LUM in combination with IVA FDC tablet orally q12h for 24 weeks.	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects received LUM 200 mg in combination with IVA 250 mg FDC tablet orally q12h for 24 weeks.	

Serious adverse events	Placebo	LUM/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 101 (10.89%)	13 / 103 (12.62%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural anxiety			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Poor venous access			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug interaction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			

subjects affected / exposed	2 / 101 (1.98%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Obstructive airways disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
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	5 / 101 (4.95%)	8 / 103 (7.77%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 101 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	LUM/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 101 (97.03%)	98 / 103 (95.15%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 101 (7.92%)	8 / 103 (7.77%)	
occurrences (all)	10	10	
Bacterial test positive			

subjects affected / exposed	8 / 101 (7.92%)	7 / 103 (6.80%)	
occurrences (all)	8	7	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 101 (5.94%)	6 / 103 (5.83%)	
occurrences (all)	6	7	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 101 (8.91%)	13 / 103 (12.62%)	
occurrences (all)	10	19	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 101 (19.80%)	15 / 103 (14.56%)	
occurrences (all)	25	16	
Fatigue			
subjects affected / exposed	11 / 101 (10.89%)	9 / 103 (8.74%)	
occurrences (all)	14	9	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 101 (6.93%)	13 / 103 (12.62%)	
occurrences (all)	7	13	
Abdominal pain			
subjects affected / exposed	10 / 101 (9.90%)	10 / 103 (9.71%)	
occurrences (all)	12	12	
Nausea			
subjects affected / exposed	9 / 101 (8.91%)	10 / 103 (9.71%)	
occurrences (all)	11	11	
Vomiting			
subjects affected / exposed	10 / 101 (9.90%)	10 / 103 (9.71%)	
occurrences (all)	11	11	
Diarrhoea			
subjects affected / exposed	4 / 101 (3.96%)	6 / 103 (5.83%)	
occurrences (all)	4	6	
Constipation			
subjects affected / exposed	8 / 101 (7.92%)	5 / 103 (4.85%)	
occurrences (all)	8	5	
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	47 / 101 (46.53%)	46 / 103 (44.66%)	
occurrences (all)	71	64	
Productive cough			
subjects affected / exposed	6 / 101 (5.94%)	18 / 103 (17.48%)	
occurrences (all)	7	21	
Nasal congestion			
subjects affected / exposed	8 / 101 (7.92%)	17 / 103 (16.50%)	
occurrences (all)	9	20	
Oropharyngeal pain			
subjects affected / exposed	10 / 101 (9.90%)	15 / 103 (14.56%)	
occurrences (all)	12	20	
Sputum increased			
subjects affected / exposed	2 / 101 (1.98%)	11 / 103 (10.68%)	
occurrences (all)	2	11	
Rhinorrhoea			
subjects affected / exposed	5 / 101 (4.95%)	10 / 103 (9.71%)	
occurrences (all)	6	14	
Respiration abnormal			
subjects affected / exposed	4 / 101 (3.96%)	6 / 103 (5.83%)	
occurrences (all)	4	8	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 101 (0.99%)	6 / 103 (5.83%)	
occurrences (all)	1	6	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	16 / 101 (15.84%)	13 / 103 (12.62%)	
occurrences (all)	23	16	
Upper respiratory tract infection			
subjects affected / exposed	10 / 101 (9.90%)	13 / 103 (12.62%)	
occurrences (all)	13	15	
Rhinitis			
subjects affected / exposed	5 / 101 (4.95%)	6 / 103 (5.83%)	
occurrences (all)	7	7	

Nasopharyngitis			
subjects affected / exposed	8 / 101 (7.92%)	5 / 103 (4.85%)	
occurrences (all)	13	7	
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 101 (7.92%)	5 / 103 (4.85%)	
occurrences (all)	9	6	
Influenza			
subjects affected / exposed	6 / 101 (5.94%)	4 / 103 (3.88%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 101 (5.94%)	3 / 103 (2.91%)	
occurrences (all)	7	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2015	Added serial post-dose spirometry assessments; added an additional PK sample.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported