



Clinical trial results:

A Phase 4, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study of the Effect of Lumacaftor/Ivacaftor Combination Therapy on Exercise Tolerance in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation.

Summary

EudraCT number	2016-000066-34
Trial protocol	GB
Global end of trial date	23 October 2017

Results information

Result version number	v1 (current)
This version publication date	02 February 2019
First version publication date	02 February 2019

Trial information

Trial identification

Sponsor protocol code	VX15-809-112
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02875366
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Clinical Trials and Medical Info, Medical Monitor, Vertex Pharmaceuticals Incorporated, 001 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Clinical Trials and Medical Info, Medical Monitor, Vertex Pharmaceuticals Incorporated, 001 617-341-6777, 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	29 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2017
Global end of trial reached?	Yes
Global end of trial date	23 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of LUM/IVA on exercise tolerance in subjects with CF, homozygous for the F508del-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	01 August 2016
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	Australia: 67
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	70
EEA total number of subjects	3

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)	22
Adults (18-64 years)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were randomized at 13 sites in Australia and the UK.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to lumacaftor (LUM)/ivacaftor (IVA) fixed-dose combination every 12 hours (q12h) for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to LUM/IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to LUM/IVA fixed-dose combination q12h for 24 weeks.

Arm title	LUM/IVA
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Arm description:

Subjects received LUM 400 mg/IVA 250 mg fixed-dose combination q12h for 24 weeks.

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

Dosage and administration details:

Subjects received LUM 400 mg/IVA 250 mg fixed-dose combination q12h for 24 weeks.

Number of subjects in period 1	Placebo	LUM/IVA
Started	36	34
Completed	36	31
Not completed	0	3
Adverse Event	-	2

Noncompliance	-	1
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Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to lumacaftor (LUM)/ivacaftor (IVA) fixed-dose combination every 12 hours (q12h) for 24 weeks.	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects received LUM 400 mg/IVA 250 mg fixed-dose combination q12h for 24 weeks.	

Reporting group values	Placebo	LUM/IVA	Total
Number of subjects	36	34	70
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	26.1	24.9	
standard deviation	± 10.58	± 10.17	-
Gender categorical			
Units: Subjects			
Female	18	13	31
Male	18	21	39
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	36	34	70
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	36	34	70
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received placebo matched to lumacaftor (LUM)/ivacaftor (IVA) fixed-dose combination every 12 hours (q12h) for 24 weeks.	
Reporting group title	LUM/IVA
Reporting group description: Subjects received LUM 400 mg/IVA 250 mg fixed-dose combination q12h for 24 weeks.	

Primary: Relative (Percent) Change From Baseline in Maximal Oxygen Consumption (VO2max) During Cardiopulmonary Exercise Testing (CPET) at Week 24

End point title	Relative (Percent) Change From Baseline in Maximal Oxygen Consumption (VO2max) During Cardiopulmonary Exercise Testing (CPET) at Week 24
End point description: CPET was used to assess change in exercise tolerance, as measured by VO2max. The Full Analysis Set (FAS) included all randomized subjects who received any amount of study drug. Here "Number of subjects analysed" signifies those subjects who were evaluated for this end point.	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: percent change				
least squares mean (confidence interval 95%)	-3.5 (-7.7 to 0.8)	-6.6 (-11.3 to -2.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3021
Method	Mixed effects model for repeated measure
Parameter estimate	Least squares mean difference
Point estimate	-3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	2.9

Secondary: Relative (Percent) Change From Baseline in Exercise Duration During CPET at Week 24

End point title	Relative (Percent) Change From Baseline in Exercise Duration During CPET at Week 24
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End point description:

Exercise duration is defined as the time at the termination of CPET exercise minus the corresponding time when CPET starts for each CPET exercise. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: percent change				
least squares mean (confidence interval 95%)	0.4 (-3.0 to 3.8)	-2.8 (-6.5 to 1.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1894
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	1.6

Secondary: Absolute Change From Baseline in Exercise Duration During CPET at Week 24

End point title	Absolute Change From Baseline in Exercise Duration During CPET at Week 24
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End point description:

Exercise duration is defined as the time at the termination of CPET exercise minus the corresponding time when CPET starts for each CPET exercise. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: seconds				
least squares mean (confidence interval 95%)	-2.1 (-20.0 to 15.9)	-17.4 (-37.2 to 2.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	LUM/IVA v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2328
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.8
upper limit	10.1

Secondary: Absolute Change From Baseline in VO2max During CPET at Week 24

End point title	Absolute Change From Baseline in VO2max During CPET at Week 24
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End point description:

CPET was used to assess change in exercise tolerance, as measured by VO2max. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: milliliter per kilogram per minute				
least squares mean (confidence interval 95%)	-1.3 (-2.5 to -0.1)	-2.7 (-4.0 to -1.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1203
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.4

Secondary: Absolute Change From Baseline in Oxygen Consumption (VO2) at Anaerobic Threshold at Week 24

End point title	Absolute Change From Baseline in Oxygen Consumption (VO2) at Anaerobic Threshold at Week 24
End point description:	Anaerobic threshold was defined as the exercise intensity at which lactate starts to accumulate. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	25		
Units: milliliter per minute				
least squares mean (confidence interval 95%)	94.6 (-5.8 to 195.0)	-55.1 (-168.0 to 57.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0439
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-149.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-295
upper limit	-4.2

Secondary: Relative (Percent) Change From Baseline in VO2 at Anaerobic Threshold at Week 24

End point title	Relative (Percent) Change From Baseline in VO2 at Anaerobic Threshold at Week 24
End point description: Anaerobic threshold was defined as the exercise intensity at which lactate starts to accumulate. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	25		
Units: percent change				
least squares mean (confidence interval 95%)	9.4 (0.9 to 17.8)	1.8 (-7.7 to 11.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2237
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	4.7

Secondary: Absolute Change From Baseline in Functional VO2 Gain at Week 24

End point title	Absolute Change From Baseline in Functional VO2 Gain at Week 24
End point description: Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: milliliter per minute per watt				
least squares mean (confidence interval 95%)	0.07 (-0.29 to 0.43)	-0.53 (-0.93 to -0.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0226
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	-0.09

Secondary: Relative (Percent) Change From Baseline in Functional VO2 Gain at Week 24

End point title	Relative (Percent) Change From Baseline in Functional VO2 Gain at Week 24
End point description: Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	26		
Units: percent change				
least squares mean (confidence interval 95%)	1.46 (-3.10 to 6.03)	-4.85 (-9.93 to 0.22)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0613
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.94
upper limit	0.31

Secondary: Absolute Change From Baseline in Pulmonary Ventilation (VE) Versus Carbon Dioxide Production (VCO2) Slope at Week 24

End point title	Absolute Change From Baseline in Pulmonary Ventilation (VE) Versus Carbon Dioxide Production (VCO2) Slope at Week 24
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End point description:

Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	26		
Units: ratio				
least squares mean (confidence interval 95%)	0.5 (-0.3 to 1.4)	0.8 (-0.1 to 1.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6409
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.5

Secondary: Relative (Percent) Change From Baseline in Pulmonary Ventilation (VE)

Versus Carbon Dioxide Production (VCO2) Slope at Week 24

End point title	Relative (Percent) Change From Baseline in Pulmonary Ventilation (VE) Versus Carbon Dioxide Production (VCO2) Slope at Week 24
End point description: Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	26		
Units: percent change				
least squares mean (confidence interval 95%)	2.0 (-0.7 to 4.6)	3.0 (0.1 to 5.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Relative (Percent) Change From Baseline in Pulmonary Ventilation (VE) Versus Carbon Dioxide Production (VCO2) Slope at Week 24. Analysis was performed using MMRM model.	
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5889
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	4.7

Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Week 24

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Week 24
End point description: FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: percentage of predicted FEV1				
least squares mean (confidence interval 95%)	-4.0 (-7.3 to -0.7)	-0.6 (-4.0 to 2.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	8.1

Secondary: Relative (Percent) Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Week 24

End point title	Relative (Percent) Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Week 24
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: percent change				
least squares mean (confidence interval 95%)	-5.4 (-10.3 to -0.5)	-1.8 (-6.9 to 3.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3091
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	10.4

Secondary: Absolute Change From Baseline in Body Mass Index (BMI) at Week 24

End point title	Absolute Change From Baseline in Body Mass Index (BMI) at Week 24
End point description:	
BMI was defined as weight in kilograms (kg) divided by height in square meter (m ²). Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	30		
Units: kg/m ²				
least squares mean (confidence interval 95%)	0.3 (0.0 to 0.6)	0.5 (0.1 to 0.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3961
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.6

Secondary: Relative (Percent) Change From Baseline in BMI at Week 24

End point title	Relative (Percent) Change From Baseline in BMI at Week 24
End point description:	BMI was defined as weight in kg divided by height in m ² . Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	30		
Units: percent change				
least squares mean (confidence interval 95%)	1.5 (0.0 to 3.1)	2.5 (0.9 to 4.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	LUM/IVA v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3905
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	3.1

Secondary: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score at Week 24

End point title	Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score at Week 24
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End point description:

The CFQ-R assessed respiratory symptoms on a scale with scores ranging from 0 to 100; where higher scores indicated fewer symptoms and better health-related quality of life. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	30		
Units: units on a scale				
least squares mean (confidence interval 95%)	-6.1 (-11.7 to -0.5)	0.1 (-5.9 to 6.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v LUM/IVA
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.1257
Method	Mixed effects model for repeated measure
Parameter estimate	Least Squares Mean Difference
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	14.1

Notes:

[1] - Analysis was performed using MMRM model.

Secondary: Number of Subjects in Each Severity Category of Patient Health Questionnaire (PHQ-8)

End point title	Number of Subjects in Each Severity Category of Patient Health Questionnaire (PHQ-8)
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End point description:

The PHQ-8 is an eight item self-reported measure of depression. Each item is rated on a scale ranging from 0 (not at all) to 3 (nearly every day). Total score is the sum of individual eight items and ranges from 0 to 24, with higher scores indicating more severe depression symptoms. Total score of 0 to 5 indicates none to minimal depression, 6 to 10 indicates mild depression, 11 to 15 indicates moderate depression, 16 to 20 indicates moderately severe depression and 21 to 24 indicates severe depression. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: subjects				
number (not applicable)				
Baseline: None to minimal (n=36,34)	27	28		
Baseline: Mild (n= 36,34)	8	5		
Baseline: Moderate (n=36,34)	0	1		
Baseline: Moderately severe (n=36,34)	1	0		
Baseline: Severe (n=36,34)	0	0		
Week 24: None to minimal (n=33,30)	23	24		
Week 24: Mild (n=33,30)	8	3		
Week 24: Moderate (n=33,30)	1	3		
Week 24: Moderately severe (n=33,30)	1	0		
Week 24: Severe (n=33,30)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Each Severity Category of Generalized Anxiety Disorder (GAD-7) Scores

End point title	Number of Subjects in Each Severity Category of Generalized Anxiety Disorder (GAD-7) Scores
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End point description:

The GAD-7 is a seven item, self-reported measurement of GAD severity. Each item is rated on a scale ranging from 0 (not at all) to 3 (nearly every day). Total score is the sum of individual seven items and ranges from 0 to 21, with higher scores indicating more severe anxiety symptoms. Total score of 0 to 5 indicates none to minimal anxiety, 6 to 10 indicates mild anxiety, 11 to 15 indicates moderate anxiety, 16 to 21 indicates severe anxiety. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: subjects				
number (not applicable)				
Baseline: None to minimal (n=36,34)	31	29		
Baseline: Mild (n=36,34)	5	5		
Baseline: Moderate (n=36,34)	0	0		
Baseline: Severe (n=36,34)	0	0		
Week 24: None to minimal (n=33,30)	26	26		
Week 24: Mild (n=33,30)	6	3		
Week 24: Moderate (n=33,30)	1	1		
Week 24: Severe (n=33,30)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Physical Activity as Determined by Actigraphy at Week 24

End point title	Absolute Change From Baseline in Physical Activity as Determined by Actigraphy at Week 24
End point description:	Subjects were provided with a wrist-worn actigraphy device which continuously collected data about daily physical activities. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.
End point type	Secondary
End point timeframe:	Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: physical activity counts				
arithmetic mean (standard deviation)	-23239 (\pm 73936.4)	-22409 (\pm 52450.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative (Percent) Change From Baseline in Physical Activity as Determined by Actigraphy at Week 24

End point title	Relative (Percent) Change From Baseline in Physical Activity as Determined by Actigraphy at Week 24
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End point description:

Subjects were provided with a wrist-worn actigraphy device which continuously collected data about daily physical activities. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: percent change				
arithmetic mean (standard deviation)	-5 (\pm 26.9)	-7 (\pm 24.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Duration of Sleep Time at Week 24

End point title	Absolute Change From Baseline in Duration of Sleep Time at Week 24
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End point description:

Subjects were provided with a wrist-worn actigraphy device which continuously collected data about sleep duration and quality. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: hours				
arithmetic mean (standard deviation)	-0.4 (\pm 0.88)	0.1 (\pm 0.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative (Percent) Change From Baseline in Duration of Sleep Time at Week 24

End point title	Relative (Percent) Change From Baseline in Duration of Sleep Time at Week 24
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End point description:

Subjects were provided with a wrist-worn actigraphy device which continuously collected data about sleep duration and quality. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent change				
arithmetic mean (standard deviation)	-5.7 (\pm 12.30)	1.5 (\pm 9.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Time Above Sedentary Duration at Week 24

End point title	Absolute Change From Baseline in Time Above Sedentary Duration at Week 24
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End point description:

Subjects were provided with a wrist-worn actigraphy device which continuously collected data about daily activities and sleep duration and quality. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	21		
Units: hours				
arithmetic mean (standard deviation)	-0.7 (\pm 1.48)	-0.7 (\pm 2.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative (Percent) Change From Baseline in Time Above Sedentary Duration at Week 24

End point title	Relative (Percent) Change From Baseline in Time Above Sedentary Duration at Week 24
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End point description:

Subjects were provided with a wrist-worn actigraphy device which continuously collected data about daily activities and sleep duration and quality. Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	21		
Units: percent change				
arithmetic mean (standard deviation)	0.2 (± 64.7)	2.3 (± 77.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)
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End point description:

Analysis was performed on FAS. Here, "Number of subjects analysed" signifies subjects who were evaluable for this end point.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	Placebo	LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: subjects				
number (not applicable)				
Subjects With AEs	35	30		
Subjects With SAEs	9	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 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:

Subjects received placebo matched to LUM/IVA fixed-dose combination tablet orally q12h for 24 weeks.

Reporting group title	LUM/IVA
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Reporting group description:

Participants received LUM 400 mg/IVA 250 mg fixed-dose combination tablet orally q12h for 24 weeks.

Serious adverse events	Placebo	LUM/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 36 (25.00%)	15 / 34 (44.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
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 / 36 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	1 / 36 (2.78%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	6 / 36 (16.67%)	8 / 34 (23.53%)	
occurrences causally related to treatment / all	0 / 7	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 36 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	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	27 / 36 (75.00%)	19 / 34 (55.88%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 36 (2.78%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Bacterial test positive			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Blood iron decreased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Fungal test positive			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 36 (5.56%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Gastrointestinal disorders			

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	3 / 34 (8.82%) 3	
Nausea subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 6	3 / 34 (8.82%) 3	
Toothache subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 34 (5.88%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4	1 / 34 (2.94%) 1	
Constipation subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 10	5 / 34 (14.71%) 5	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	0 / 34 (0.00%) 0	
Haemoptysis subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 4	3 / 34 (8.82%) 3	
Increased viscosity of bronchial secretion subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	3 / 34 (8.82%) 3	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	1 / 34 (2.94%) 1	
Productive cough subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 4	1 / 34 (2.94%) 1	
Respiration abnormal			

subjects affected / exposed occurrences (all)	9 / 36 (25.00%) 9	5 / 34 (14.71%) 7	
Sputum increased subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 6	2 / 34 (5.88%) 2	
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 34 (5.88%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 7	8 / 34 (23.53%) 10	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 5	4 / 34 (11.76%) 4	
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3	3 / 34 (8.82%) 4	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	1 / 34 (2.94%) 1	
Sinusitis subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 34 (0.00%) 0	

Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4	0 / 34 (0.00%) 0	
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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