Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study of the Efficacy, Safety, and Pharmacokinetics of Intravenous Ulimorelin (LP101) in Patients with Enteral Feeding Intolerance

Summary

EudraCT number	2016-000723-94
Trial protocol	ES NL
Global end of trial date	09 March 2018

Results information

Result version number	v1 (current)
This version publication date	10 August 2018
First version publication date	10 August 2018

Trial information

Trial identification

Sponsor protocol code	LP101-CL-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02784392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lyric Pharmaceuticals, Inc.
Sponsor organisation address	601 Gateway Blvd, Suite 1020, South San Francisco, United States, CA94080
Public contact	David Wurtman, Lyric Pharmaceuticals Inc., david@lyricpharma.com
Scientific contact	David Wurtman, Lyric Pharmaceuticals Inc., david@lyricpharma.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2018
Global end of trial reached?	Yes
Global end of trial date	09 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of multiple daily intravenous (IV) doses of ulimorelin on the proportion of the target daily protein received through enteral nutrition by mechanically ventilated and tube-fed patients with enteral feeding intolerance (EFI).

It is noted that only the results of the efficacy phase are reported within this dataset.

Protection of trial subjects:

A single consent form was used for both study phases. To allow a seamless transition from the Observation Phase to the Efficacy Phase, patients screened for the Observation Phase provided informed consent (by proxy if the patient was unable to provide valid informed consent) for both the Observation Phase and Efficacy Phase and transitioned immediately to the Efficacy Phase if enteral feeding intolerance (EFI) develops. Patients who did not participate in the Observation Phase only provided informed consent (by proxy if necessary) for the Efficacy Phase. Patients who participated in the Observation Phase but who did not transition to the Efficacy Phase within 24 hours of completing the Observation Phase were required to provide a new informed consent if they became eligible for and wished to participate in the Efficacy Phase at a later point in time. Whenever possible, patients who participated in either study phase based on proxy consent were re-consented once deemed capable by the Investigator of providing consent on their own.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 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	Canada: 8
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Spain: 62
Worldwide total number of subjects	122
EEA total number of subjects	95

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)	76
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

To be eligible for the Efficacy Phase, patients must have been intolerant to continuous gastric tube feedings (Gastric Residual Volume >= 500 mL).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Efficacy phase - Ulimorelin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ulimorelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ulimorelin 600 µg/kg was diluted with dextrose in water 5% to a total delivery volume of 50 mL, for IV infusion Q8H for 15 doses (5 days), although higher volumes could be prepared depending on the priming volume of the infusion pump. The infusion should be administered at a rate of 1.67 mL/min for a total of 30 minutes. Dosing was based on the patient’s estimated dry body weight at ICU admission.

Arm title	Efficacy phase - Metoclopramide

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Metoclopramide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Metoclopramide 10 mg was diluted with dextrose in water 5% to a total delivery volume of 50 mL, for IV infusion Q8H for 15 doses (5 days), although higher volumes could be prepared depending on the priming volume of the infusion pump. The infusion should be administered at a rate of 1.67 mL/min for a total of 30 minutes. Dosing was based on the patient’s estimated dry body weight at ICU admission.

Number of subjects in period 1	Efficacy phase - Ulimorelin	Efficacy phase - Metoclopramide
Started	63	59
Completed	39	42
Not completed	24	17
Adverse event, serious fatal	4	1
Discontinuation of tube feedings	2	1
Treatment success	5	3
Failure of tube feedings	8	4
Adverse event, non-fatal	1	3
Other reasons	2	3
Events related to underlying conditions	1	1
Not dosed	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	122	122	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	76	76	
From 65-84 years	46	46	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	33	33	
Male	89	89	

End points

End points reporting groups

Reporting group title	Efficacy phase - Ulimorelin
Reporting group description: -	
Reporting group title	Efficacy phase - Metoclopramide
Reporting group description: -	

Primary: Daily average (mean) percentage of daily protein prescription received through enteral nutrition during Efficacy Phase Days 1 through 5

End point title	Daily average (mean) percentage of daily protein prescription received through enteral nutrition during Efficacy Phase Days 1 through 5
End point description:	

End point type	Primary
End point timeframe:	
Days 1-5 of Efficacy Phase	

End point values	Efficacy phase - Ulimorelin	Efficacy phase - Metoclopramide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Percentage				
arithmetic mean (standard deviation)				
Day 1	65.5 (± 40.3)	71.6 (± 35.7)		
Day 2	74.4 (± 39.3)	71.3 (± 37.8)		
Day 3	74.0 (± 44.1)	81.1 (± 40.4)		
Day 4	67.0 (± 47.5)	80.5 (± 36.2)		
Day 5	65.1 (± 47.2)	72.5 (± 43.0)		
Average Days 1 to 5	68.4 (± 38.5)	75.1 (± 30.7)		

Statistical analyses

Statistical analysis title	Difference between treatment groups
Comparison groups	Efficacy phase - Ulimorelin v Efficacy phase - Metoclopramide
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4878 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Analysis of statistical significance of difference between treatment groups.

[2] - P value for difference between averages for Days 1 to 5.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) reported during the efficacy phase from time of consent through to 3 days after the final dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Ulimorelin
Reporting group description: -	
Reporting group title	Metoclopramide

Reporting group description: -

Serious adverse events	Ulimorelin	Metoclopramide	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 62 (4.84%)	3 / 58 (5.17%)	
number of deaths (all causes)	12	4	
number of deaths resulting from adverse events	3	1	
Injury, poisoning and procedural complications			
Blood stem cell transplant failure			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Overdose			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			

subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	
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			
Obstructive airways disorder			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Restrictive pulmonary disease			
subjects affected / exposed	1 / 62 (1.61%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Ulimorelin	Metoclopramide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 62 (70.97%)	37 / 58 (63.79%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 62 (1.61%)	4 / 58 (6.90%)	
occurrences (all)	1	4	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Liver function test abnormal			
subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Vascular disorders			

Hypertension			
subjects affected / exposed	3 / 62 (4.84%)	4 / 58 (6.90%)	
occurrences (all)	3	4	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	3 / 62 (4.84%)	1 / 58 (1.72%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	5 / 62 (8.06%)	5 / 58 (8.62%)	
occurrences (all)	5	5	
Pyrexia			
subjects affected / exposed	4 / 62 (6.45%)	3 / 58 (5.17%)	
occurrences (all)	4	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 62 (9.68%)	5 / 58 (8.62%)	
occurrences (all)	6	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 62 (3.23%)	4 / 58 (6.90%)	
occurrences (all)	2	4	
Diarrhoea			
subjects affected / exposed	3 / 62 (4.84%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
Vomiting			
subjects affected / exposed	4 / 62 (6.45%)	0 / 58 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	9 / 62 (14.52%)	6 / 58 (10.34%)	
occurrences (all)	9	6	
Agitation			
subjects affected / exposed	7 / 62 (11.29%)	3 / 58 (5.17%)	
occurrences (all)	7	3	
Anxiety			

subjects affected / exposed	1 / 62 (1.61%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	8 / 62 (12.90%)	8 / 58 (13.79%)	
occurrences (all)	8	8	
Hypophosphataemia			
subjects affected / exposed	4 / 62 (6.45%)	1 / 58 (1.72%)	
occurrences (all)	4	1	
Hypernatraemia			
subjects affected / exposed	3 / 62 (4.84%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
Hypokalaemia			
subjects affected / exposed	3 / 62 (4.84%)	1 / 58 (1.72%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2016	Amendment 1, protocol version 2, modified the exclusion criteria, removed stratification by site, deleted an interim analysis and added a sensitivity analysis, and made administrative changes. The protocol amendment was made prior to initiation of the study.
28 June 2016	Amendment 2, protocol version 3, modified and/or clarified study procedures including timing of switch to protocol compliant enteral feeding formula, assessment of 30-day mortality, use and timing of propofol, GRV measurements, timing and analysis of dialysis sample collection, and assessment period for pulmonary infections. The amendment also made other administrative changes.
23 November 2016	Amendment 3, protocol version 4, added the separate Observation Phase in order to explore factors associated with the progression of at-risk patients to EFI.
05 July 2017	Amendment 4, protocol version 5, added 2 metabolic exploratory measures to measure changes in 3-O-MG and D3-creatine dilution to assess nutrient absorption and muscle mass. The amendment also provided for a rephrasing of the primary endpoint, a modification of the exclusion for QT interval prolongation, and a provision for following patients with 3-fold or greater transaminase elevations in liver function tests on Day 3 or Day 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For non-serious adverse events only the number of subjects experiencing each event were reported, not number of occurrences. Therefore the number of occurrences is entered as the number of subjects experiencing the event.

Notes: