Clinical trial results:
A Double-Blinded, Multi-Center, Randomized, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) in the Treatment of Restless Legs Syndrome (RLS)

Summary

EudraCT number	2015-001521-16
Trial protocol	HU CZ PL ES
Global end of trial date	02 January 2018

Results information

Result version number	v1 (current)
This version publication date	24 April 2021
First version publication date	24 April 2021
Summary attachment (see zip file)	2015-001521-16_CSR Synopsis_26Nov2018 (2015-001521-16_CSR Synopsis_26Nov2018.pdf)

Trial information

Trial identification

Sponsor protocol code	1VIT14037

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02397057
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Luitpold Pharmaceuticals, Inc.
Sponsor organisation address	800 Adams Avenue, Norristown, United States, PA 19403
Public contact	Mark Falone, American Regent, mfalone@americanregent.com
Scientific contact	Mark Falone, American Regent, mfalone@americanregent.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	10 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2018
Global end of trial reached?	Yes
Global end of trial date	02 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of an IV Injectafer® in subjects with Restless Leg Syndrome (RLS).

Protection of trial subjects:

Subjects were informed by the Investigator about the nature of the study, along with the aims, methods, anticipated benefits, potential hazards, and discomfort that participation may have entailed. Written informed consent was obtained from subjects. The study protocol and the informed consent form were submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 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	Poland: 52
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Ukraine: 44
Worldwide total number of subjects	209
EEA total number of subjects	89

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)	142
From 65 to 84 years	66
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in the US and Europe between 19 February 2015 and 22 January 2017.

Pre-assignment

Screening details:

The screening period, starting at Day -7 and following obtainment of informed consent/assent, was of maximum 9 days to allow for all screening results to be obtained and validated.

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, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment

Arm description:

On Day 0 and Day 5, subjected received 750 mg active investigational medicinal product, Injectafer®, intravenously at 100 mg/mL.

Arm type	Experimental
Investigational medicinal product name	Injectafer®
Investigational medicinal product code	Injectafer®
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

750 mg solution for intravenous administration

Arm title	Placebo

Arm description:

On Day 0 and Day 5, subjects received 15 mL placebo (standard saline solution) IV push.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 ml, IV push

Number of subjects in period 1	Active treatment	Placebo
Started	105	104
Completed	94	91
Not completed	11	13
Consent withdrawn by subject	6	7
Physician decision	-	1
Death	1	-
Not specified	-	1
Adverse event	-	1
Lost to follow-up	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Active treatment
Reporting group description:	
On Day 0 and Day 5, subjected received 750 mg active investigational medicinal product, Injectafer®, intravenously at 100 mg/mL.	
Reporting group title	Placebo
Reporting group description:	
On Day 0 and Day 5, subjects received 15 mL placebo (standard saline solution) IV push.	

Reporting group values	Active treatment	Placebo	Total
Number of subjects	105	104	209
Age categorical			
Mean age of all subjects was 57.6 years (23 years to 85 years).			
Units: Subjects			
Adults (18-64 years)	71	71	142
From 65-84 years	34	32	66
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	70	71	141
Male	35	33	68

End points

End points reporting groups

Reporting group title	Active treatment
Reporting group description:	
On Day 0 and Day 5, subjected received 750 mg active investigational medicinal product, Injectafer®, intravenously at 100 mg/mL.	
Reporting group title	Placebo
Reporting group description:	
On Day 0 and Day 5, subjects received 15 mL placebo (standard saline solution) IV push.	

Primary: IRLS total score

End point title	IRLS total score
End point description:	
Change in IRLS total score from baseline to Day 42.	
End point type	Primary
End point timeframe:	
Baseline Day 42	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[1]	103[2]		
Units: n/a				
least squares mean (confidence interval 95%)	-8.0 (-9.6 to -6.4)	-4.8 (-6.5 to -3.2)		

Notes:

[1] - 2 subjects in placebo group treated with active substances but not analyzed in FAS

[2] - 2 subjects in placebo group treated with active substances but not analyzed in FAS

Statistical analyses

Statistical analysis title	IRLS total score
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0043
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 0 to Day 365	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Active treatment
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Active treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 107 (5.61%)	4 / 101 (3.96%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer stage IV			
subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 107 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 107 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 107 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 107 (0.93%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Active treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 107 (67.29%)	34 / 101 (33.66%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 107 (4.67%)	1 / 101 (0.99%)	
occurrences (all)	5	1	
Blood pressure increased			
subjects affected / exposed	5 / 107 (4.67%)	1 / 101 (0.99%)	
occurrences (all)	5	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 107 (2.80%)	1 / 101 (0.99%)	
occurrences (all)	3	1	
Blood phosphorus decreased			
subjects affected / exposed	3 / 107 (2.80%)	0 / 101 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyl transferase increased			
subjects affected / exposed	3 / 107 (2.80%)	3 / 101 (2.97%)	
occurrences (all)	3	3	
Vascular disorders			
Flushing			
subjects affected / exposed	6 / 107 (5.61%)	0 / 101 (0.00%)	
occurrences (all)	6	0	
Hot flush			
subjects affected / exposed	5 / 107 (4.67%)	1 / 101 (0.99%)	
occurrences (all)	5	1	
Hypertension			
subjects affected / exposed	0 / 107 (0.00%)	3 / 101 (2.97%)	
occurrences (all)	0	3	

Nervous system disorders			
Headache			
subjects affected / exposed	5 / 107 (4.67%)	6 / 101 (5.94%)	
occurrences (all)	5	9	
Paraestesia			
subjects affected / exposed	3 / 107 (2.80%)	1 / 101 (0.99%)	
occurrences (all)	3	1	
Dizziness			
subjects affected / exposed	8 / 107 (7.48%)	1 / 101 (0.99%)	
occurrences (all)	8	1	
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	6 / 107 (5.61%)	0 / 101 (0.00%)	
occurrences (all)	6	0	
Fatigue			
subjects affected / exposed	4 / 107 (3.74%)	0 / 101 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 107 (9.35%)	1 / 101 (0.99%)	
occurrences (all)	12	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 107 (2.80%)	1 / 101 (0.99%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 107 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 107 (0.93%)	2 / 101 (1.98%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	2 / 107 (1.87%)	0 / 101 (0.00%)	
occurrences (all)	2	0	

Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 107 (3.74%)	4 / 101 (3.96%)	
occurrences (all)	4	4	
Upper respiratory tract infection			
subjects affected / exposed	4 / 107 (3.74%)	1 / 101 (0.99%)	
occurrences (all)	4	1	
Respiratory tract infection			
subjects affected / exposed	3 / 107 (2.80%)	3 / 101 (2.97%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	8 / 107 (7.48%)	1 / 101 (0.99%)	
occurrences (all)	9	1	
Decreased appetite			
subjects affected / exposed	4 / 107 (3.74%)	0 / 101 (0.00%)	
occurrences (all)	4	0	
Hyperglycaemia			
subjects affected / exposed	3 / 107 (2.80%)	2 / 101 (1.98%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2015	Amendment (13 July 2015) included the following key changes: • Day 28 was added to the remote contact by phone procedure. • Interactive Web Response/Electronic Data Capture was updated to IRT. • The C-SSRS was added. • Stratification of subjects by RLS medication-related augmentation was added. • Definition of intervention was updated. • RLS therapy prior to screening was revised to specify subjects should be on monotherapy for RLS. Exclusion criterion #5 (subjects with multiple sclerosis) was added. • Stratification factor for the CMH test was changed to region (US, EUR). • Information on the natural history, disease understanding, and treatment guidance for RLS was updated. • Length of the study was adjusted from approximately 12½ months to approximately 12 months. • Procedure for tapering from current RLS medication posttreatment was added. • An RLS subject diary to record progress was added to the study procedures. • The following study procedures were added to Day 365 (End of Study): o Contact IRT to complete subject from study. o If the subject terminated early or the Day 365 phosphorus value was below the lower limit of normal, the subject should have returned (as directed by the Investigator) for a repeat blood sample until the value was back within normal limits. • Reporting of SAEs was updated to specify any SAE was to be reported within 24 hours of the Investigator becoming aware of the event. Time off pre-enrollment prescribed RLS medications was added to the secondary efficacy endpoints
02 June 2016	Amendment (02 June 2016) included the following key changes: • Further details were added to the RLS tapering treatment regimen: o Day 6 was added to the timing of tapering from prescribed RLS medication. o The subject was to be maintained on the lowest dose level attained at the end of the tapering period and that dose was to remain stable for the duration of the subject's participation in the study. • A +2-day window was added to the 7-day screening period. • The time frame for keeping the RLS diary was updated to starting at screening. • Additional dosing details were revised to specify that central laboratory results obtained during the Day 42 or Day 168 visit could have been used to qualify a subject for additional dosing if those laboratory tests had occurred with 14 days of the first dose of study drug. • An interim analysis of efficacy was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported