Clinical trial results:
A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)

Summary

EudraCT number	2015-002448-15
Trial protocol	GB BE FI DE
Global end of trial date	07 December 2016

Results information

Result version number	v1 (current)
This version publication date	14 March 2018
First version publication date	14 March 2018

Trial information

Trial identification

Sponsor protocol code	LJ501-CRH01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02338843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	La Jolla Pharmaceutical Company
Sponsor organisation address	4550 Towne Centre Court, San Diego, United States, 92121
Public contact	Doranne Frano, La Jolla Pharmaceutical Company , 1 8584336908, dfrano@ljpc.com
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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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2016
Global end of trial reached?	Yes
Global end of trial date	07 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of the study was to compare LJPC-501 treatment versus placebo for the treatment of efficacy, safety, and tolerability in patients with CRH. The primary objective of this study was to compare the effect of LJPC-501 infusion on MAP in patients with CRH.

Protection of trial subjects:

Unblinded safety analyses were performed for review by the DSMB on 4 occasions between the first study drug administration and completion of the study. The Sponsor, the Statistician, and all study and site personnel remained blinded except for the study pharmacist(s) at each site. On each occasion, the DSMB recommended that the enrollment continue without modifications to the study protocol.
A blinded interim analysis was performed after all assessments (including 28-day follow-up) were completed for 150 patients. The efficacy analyses were performed to test data management and the analysis systems in advance of the final database lock and were not planned for decisions affecting further enrollment for futility or superior efficacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 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	Belgium: 1
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	United States: 216
Country: Number of subjects enrolled	Australia: 47
Worldwide total number of subjects	344
EEA total number of subjects	36

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)	184
From 65 to 84 years	146
85 years and over	14

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	344
Number of subjects completed	321

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Had rapid decline: 4
Reason: Number of subjects	Had rapid improvement: 10
Reason: Number of subjects	Consent withdrawn by investigator: 3
Reason: Number of subjects	Did not meet eligibility: 1
Reason: Number of subjects	Receiving drug from another study: 1
Reason: Number of subjects	Consent withdrawn by subject: 4

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LJPC-501 (angiotensin II)

Arm description:

Treatment arm
LJPC-501: Treatment arm

Arm type	Experimental
Investigational medicinal product name	LJPC-501 (angiontensin II)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Starting dose of 20 ng/kg/min (LJPC-501) administered IV; may dose escalate up to 200 ng/kg/min in order to achieve a MAP of 75 mmHg or higher. If MAP of at least 75 mmHg is achieved, study drug will be titrated to maintain the MAP between 75 and 84 mmHg until the 3-hour time point on Day 1, i.e., 3 hours from the initiation of study drug.
Prespecified dose titration and withdrawal guidelines based on MAP through 48 hours.
Continued use for up to 7 days is permitted per prespecified dose guidelines.

Arm title	Placebo (0.9% Sodium Chloride Solution)

Arm description:

Placebo arm

Placebo : PBO

Arm type	Placebo
Investigational medicinal product name	0.9% Sodium Chloride Solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal saline (0.9% Sodium Chloride solution) will be delivered in volume matched increments for placebo group.

Number of subjects in period 1[1]	LJPC-501 (angiotensin II)	Placebo (0.9% Sodium Chloride Solution)
Started	163	158
Completed	119	100
Not completed	44	58
Adverse event, serious fatal	40	53
Physician decision	1	-
Subject discontinued prior to randomization	1	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	1
Subject Recovered	-	2

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: The worldwide number of subjects enrolled in the trial includes all subjects in the pre-assignment period that were randomized but did not receive any study drug (ITT population, N=344). The number of subjects in the baseline period includes all subjects that were randomized and received study drug (mITT population, N=321). Because all efficacy and safety analyses include subjects in the mITT population, the mITT population was also used for baseline analyses for comparability.

Baseline characteristics

Reporting groups	
Reporting group title	LJPC-501 (angiotensin II)
Reporting group description:	
Treatment arm LJPC-501: Treatment arm	

Reporting group title	Placebo (0.9% Sodium Chloride Solution)
Reporting group description:	
Placebo arm Placebo : PBO	

Reporting group values	LJPC-501 (angiotensin II)	Placebo (0.9% Sodium Chloride Solution)	Total
Number of subjects	163	158	321
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	90	77	167
From 65-84 years	64	76	140
85 years and over	9	5	14
Age continuous Units: years			
median	63	65	
inter-quartile range (Q1-Q3)	52 to 75	53 to 75	-
Gender categorical Units: Subjects			
Female	71	55	126
Male	92	103	195
Region of Enrollment Units: Subjects			
New Zealand	4	5	9
Canada	26	10	36
Belgium	0	1	1
United States	90	110	200
Finland	5	2	7
United Kingdom	9	9	18
Australia	24	19	43
France	5	1	6
Germany	0	1	1
Cause of Shock Units: Subjects			

Sepsis	127	132	259
Other, potentially sepsis	20	11	31
Pancreatitis	0	2	2
Vasoplegia	10	9	19
Other	6	4	10
Mean Arterial Pressure (MAP)			
Units: mmHg			
median	66.3	66.3	
inter-quartile range (Q1-Q3)	63.7 to 69.0	63.0 to 68.3	-
APACHE II Score			
Units: Points			
median	27	29	
inter-quartile range (Q1-Q3)	22 to 33	22 to 34	-
Vasopressor Dose			
Units: mcg/kg/min			
median	0.33	0.34	
inter-quartile range (Q1-Q3)	0.23 to 0.56	0.23 to 0.56	-

End points

End points reporting groups

Reporting group title	LJPC-501 (angiotensin II)
Reporting group description:	
Treatment arm LJPC-501: Treatment arm	

Reporting group title	Placebo (0.9% Sodium Chloride Solution)
Reporting group description:	
Placebo arm Placebo : PBO	

Primary: An increased MAP, defined as achievement of a Day 1 MAP at 3 hours following the initiation of study drug, of ≥ 75 mmHg OR a 10 mmHg increase in baseline MAP without an increase in vasopressors

End point title	An increased MAP, defined as achievement of a Day 1 MAP at 3 hours following the initiation of study drug, of ≥ 75 mmHg OR a 10 mmHg increase in baseline MAP without an increase in vasopressors
End point description:	
Response with respect to mean arterial pressure (MAP) at hour 3 after the start of infusion was defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors	
End point type	Primary
End point timeframe:	
Hour 3	

End point values	LJPC-501 (angiotensin II)	Placebo (0.9% Sodium Chloride Solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	158		
Units: Participants	114	37		

Statistical analyses

Statistical analysis title	Analysis of Primary Endpoint-Logistic Regression
Statistical analysis description:	
Chi-square test from logistic regression model including LJPC-501 treatment compared to Placebo, and adjusted by baseline MAP, baseline APACHE II Score, vasopressin use 6 hours prior to randomization and mean NED over the 6 hours prior to randomization	
Comparison groups	LJPC-501 (angiotensin II) v Placebo (0.9% Sodium Chloride Solution)

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.76
upper limit	13.3

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from study drug initiation through Day 28.	
Adverse event reporting additional description:	
Not applicable.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	LJPC-501 (angiotensin II)
Reporting group description:	
Treatment arm LJPC-501: Treatment arm	
Reporting group title	Placebo (0.9% Sodium Chloride Solution)
Reporting group description:	
Placebo arm Placebo : PBO	

Serious adverse events	LJPC-501 (angiotensin II)	Placebo (0.9% Sodium Chloride Solution)	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 163 (60.74%)	106 / 158 (67.09%)	
number of deaths (all causes)	76	85	
number of deaths resulting from adverse events	76	85	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoma			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small cell carcinoma			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	3 / 163 (1.84%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distributive shock			
subjects affected / exposed	1 / 163 (0.61%)	4 / 158 (2.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Hypotension			

subjects affected / exposed	5 / 163 (3.07%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Peripheral ischaemia			
subjects affected / exposed	5 / 163 (3.07%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	2 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	3 / 163 (1.84%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Shock haemorrhagic			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasospasm			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Medical device complication			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			

subjects affected / exposed	25 / 163 (15.34%)	23 / 158 (14.56%)	
occurrences causally related to treatment / all	0 / 25	0 / 23	
deaths causally related to treatment / all	0 / 23	0 / 21	
Pyrexia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (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			
Acute pulmonary oedema			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 163 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute respiratory failure			
subjects affected / exposed	3 / 163 (1.84%)	5 / 158 (3.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 4	
Aspiration			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchomalacia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopleural fistula			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 163 (0.61%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 163 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	8 / 163 (4.91%)	11 / 158 (6.96%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 6	0 / 6	
Psychiatric disorders			
Mental status change			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactic acid increased			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcus test positive			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrostomy tube site complication			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 163 (1.23%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	5 / 163 (3.07%)	5 / 158 (3.16%)	
occurrences causally related to treatment / all	3 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 163 (0.61%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	7 / 163 (4.29%)	9 / 158 (5.70%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 3	0 / 6	
Cardiac failure			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 163 (1.84%)	5 / 158 (3.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 4	
Cardiogenic shock			
subjects affected / exposed	2 / 163 (1.23%)	4 / 158 (2.53%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 4	
Cardiopulmonary failure			

subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 163 (0.61%)	4 / 158 (2.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 163 (1.23%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	2 / 163 (1.23%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	5 / 163 (3.07%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain hypoxia			

subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	1 / 163 (0.61%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			
subjects affected / exposed	0 / 163 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of conciousness			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic leukoencephalopathy			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (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			
Anaemia			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			

subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal mucosal exfoliation			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 163 (0.61%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis necrotising			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vascular thrombosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			

subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin discolouration			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Muscle necrosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (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			
Abdominal abscess			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve vegetation			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile sepsis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Enterobacter bacteraemia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	2 / 163 (1.23%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 163 (1.84%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			

subjects affected / exposed	18 / 163 (11.04%)	10 / 158 (6.33%)	
occurrences causally related to treatment / all	0 / 18	0 / 10	
deaths causally related to treatment / all	0 / 15	0 / 9	
Tracheobronchitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	2 / 163 (1.23%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Hyperkalaemia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolic acidosis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LJPC-501 (angiotensin II)	Placebo (0.9% Sodium Chloride Solution)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 163 (67.48%)	110 / 158 (69.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 163 (5.52%)	9 / 158 (5.70%)	
occurrences (all)	11	9	
Hypotension			
subjects affected / exposed	13 / 163 (7.98%)	7 / 158 (4.43%)	
occurrences (all)	16	7	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	17 / 163 (10.43%)	16 / 158 (10.13%)	
occurrences (all)	18	18	
Bradycardia			
subjects affected / exposed	6 / 163 (3.68%)	9 / 158 (5.70%)	
occurrences (all)	6	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 163 (6.75%)	9 / 158 (5.70%)	
occurrences (all)	11	9	
Thrombocytopenia			
subjects affected / exposed	15 / 163 (9.20%)	10 / 158 (6.33%)	
occurrences (all)	15	10	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	8 / 163 (4.91%)	8 / 158 (5.06%)	
occurrences (all)	8	8	
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 163 (3.68%)	8 / 158 (5.06%)	
occurrences (all)	6	8	
Delirium			
subjects affected / exposed	9 / 163 (5.52%)	1 / 158 (0.63%)	
occurrences (all)	9	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 163 (4.91%)	10 / 158 (6.33%)	
occurrences (all)	8	11	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	13 / 163 (7.98%)	10 / 158 (6.33%)	
occurrences (all)	14	10	
Hypophosphataemia			
subjects affected / exposed	6 / 163 (3.68%)	11 / 158 (6.96%)	
occurrences (all)	6	11	

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