



Clinical trial results:

Prospective, Double-Blind, Multicenter Study Evaluating the Safety of Repeat Doses of IV Serelaxin in Subjects with Chronic Heart Failure

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2013-002781-39
Trial protocol	DE IT FI ES SE NO RO NL CZ
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CRLX030A2209
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01982292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	23 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the proportion of patients with CHF who develop anti-serelaxin antibodies at any time following repeat administration of three IV continuous infusions of serelaxin administered for up to 48 hours in four week intervals.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. The Investigator could prescribe any medications and/or supportive care during the study based on clinical needs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2014
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: 3
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Germany: 120
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	323
EEA total number of subjects	245

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)	127
From 65 to 84 years	190
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 323 patients were randomized to the serelaxin or placebo treatment in a 2:1 ratio. 2 patients from serelaxin were mis-randomized, hence 321 received study drug.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	RLX030 (serelaxin)

Arm description:

Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Arm type	Experimental
Investigational medicinal product name	serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

RLX030 (serelaxin) was administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day as a continuous IV infusion for 48 hours.

Arm title	Placebo
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Arm description:

Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Arm type	Placebo
Investigational medicinal product name	Placebo of RLX030 (serelaxin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo of serelaxin was administered as a continuous IV infusion for 48 hours.

Number of subjects in period 1	RLX030 (serelaxin)	Placebo
Started	215	108
Full analysis set (FAS)	213	108
Safety set	212	108
Completed	203	107
Not completed	12	1
Adverse event, serious fatal	1	-
Adverse event, non-fatal	2	-
Protocol Deviation	1	-
Patient/Guardian Decision	3	1
Technical Problems	2	-
Non-Compliance With Study Treatment	1	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	RLX030 (serelaxin)
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Reporting group description:

Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Reporting group title	Placebo
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Reporting group description:

Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Reporting group values	RLX030 (serelaxin)	Placebo	Total
Number of subjects	215	108	323
Age categorical Units: Subjects			
Adults (18-64 years)	79	48	127
From 65-84 years	133	57	190
85 years and over	3	3	6
Gender, Male/Female Units: Subjects			
Female	46	26	72
Male	169	82	251

End points

End points reporting groups

Reporting group title	RLX030 (serelaxin)
Reporting group description:	
Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8	
Reporting group title	Placebo
Reporting group description:	
Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8	

Primary: Percentage of participants with chronic heart failure (CHF) who develop anti-serelaxin antibodies at any time following repeat administration of IV continuous infusions of serelaxin administered for up to 48 hours in 16 weeks

End point title	Percentage of participants with chronic heart failure (CHF) who develop anti-serelaxin antibodies at any time following repeat administration of IV continuous infusions of serelaxin administered for up to 48 hours in 16 weeks
End point description:	
A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. A patient is considered antibody negative during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were negative. A patient's antibody status is considered to be undetermined during the study if it is not defined as positive or negative.	
End point type	Primary
End point timeframe:	
16 weeks	

End point values	RLX030 (serelaxin)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	106		
Units: Percentage of participants				
number (confidence interval 90%)				
Positive	0.5 (0.03 to 2.35)	0 (0 to 2.79)		
Negative	99.5 (97.65 to 99.97)	100 (97.21 to 100)		

Statistical analyses

Statistical analysis title	Difference in % of pts with +ve antibody status
Statistical analysis description:	
Difference in percentage of patients with positive antibody status	
Comparison groups	RLX030 (serelaxin) v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.9999
Method	Fisher exact
Parameter estimate	Difference in percentage
Point estimate	0.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.38
upper limit	10.38

Statistical analysis title	Difference in % of pts with - ve antibody status
Statistical analysis description:	
Difference in percentage of patients with negative antibody status	
Comparison groups	RLX030 (serelaxin) v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	-0.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.38
upper limit	9.38

Secondary: Percentage of participants with chronic heart failure who develop positive anti-serelaxin antibodies after a single infusion of serelaxin over time up to week 16

End point title	Percentage of participants with chronic heart failure who develop positive anti-serelaxin antibodies after a single infusion of serelaxin over time up to week 16
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End point description:

A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. Each time period is defined as the time frame from study drug initiation (or the visit if there is no infusion) to prior to study drug initiation of the next period (or the visit if no there is no infusion). n= The total number of subjects with evaluable antibody status during the defined period.

End point type	Secondary
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End point timeframe:

Randomization to Week 4, Week 4 to Week 8, Week 8 to Week 12, week 12 to week 16

End point values	RLX030 (serelaxin)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	108		
Units: Percentage of patients				
number (confidence interval 90%)				
Randomization to week 4 (n= 209, 107)	0.48 (0.02 to 2.25)	0 (0 to 2.76)		
Week 4 to week 8 (n= 204, 108)	0.49 (0.03 to 2.3)	0 (0 to 2.74)		
Week 8 to week 12 (n= 204, 107)	0.49 (0.03 to 2.3)	0 (0 to 2.76)		
Week 12 to week 16 (n= 2, 2)	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody titers in participants with chronic heart failure who develop anti-serelaxin antibodies (neutralizing, non-neutralizing or both) at any time following 3 repeated infusions and at Week 4, Week 8 and Week 12.

End point title	Antibody titers in participants with chronic heart failure who develop anti-serelaxin antibodies (neutralizing, non-neutralizing or both) at any time following 3 repeated infusions and at Week 4, Week 8 and Week 12.
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End point description:

End point type	Secondary
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End point timeframe:

Week 4, Week 8, Week 12

End point values	RLX030 (serelaxin)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[1]	0 ^[2]		
Units: In international Units				
arithmetic mean (standard deviation)	9999 (± 99.99)	()		

Notes:

[1] - Antibody titers unavailable as positive anti-bodies patients were very low in number

[2] - Antibody titers is unavailable because there was no positive anti-body patient

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with chronic heart failure with positive antibody status who develop non-neutralizing anti-serelaxin antibodies following 3 repeated infusions (i.e. at Week 4, Week 8, and Week 12)

End point title	Percentage of participants with chronic heart failure with positive antibody status who develop non-neutralizing anti-
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End point description:

A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. n = the total number of subjects with evaluable antibody status after specified number of infusions

End point type Secondary

End point timeframe:

At Week 4, Week 8, Week 12

End point values	RLX030 (serelaxin)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	108		
Units: Percentage of participants				
number (confidence interval 90%)				
after 1 infusion (at week 4) [n=209,108]	0.48 (0.02 to 2.25)	0 (0 to 2.74)		
after 2 infusions (at week 8) [n=200,106]	0.5 (0.03 to 2.35)	0 (0 to 2.79)		
after 3 infusions (at week 12) [n=184, 102]	0.54 (0.03 to 2.55)	0 (0 to 2.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events such as adjudicated potential hypersensitivity or infusion reactions

End point title Number of participants with adverse events such as adjudicated potential hypersensitivity or infusion reactions

End point description:

Incidence rate of special interest, indicative of hypersensitivity reactions which occur during and after administration of repeated infusions of serelaxin relative to placebo in subjects with chronic heart failure is reported. Hypersensitivity reactions or infusion reactions can be headache, nausea, fever, chills, dizziness, flush, pruritus, chest and/or back pain.

End point type Secondary

End point timeframe:

16 weeks

End point values	RLX030 (serelaxin)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	108		
Units: Participants				
Submitted for adjudication	32	14		

Confirmed with no hypersensitivity reactions	32	14		
Hypersensitivity reactions confirmed	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of RLX030: Area under the plasma concentration time curve from time zero up to 48 hours post dose (AUC 0-48)

End point title	Pharmacokinetics of RLX030: Area under the plasma concentration time curve from time zero up to 48 hours post dose (AUC 0-48) ^[3]
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End point description:

Due to sparse PK sampling, AUC 0-48 hours was not analyzed.

End point type	Secondary
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End point timeframe:

pre-infusion and 8, 24 and 48 hours post each infusion.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK gets measured on study drug, not on placebo

End point values	RLX030 (serelaxin)			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[4]			
Units: h*ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[4] - Due to sparse PK sampling, AUC 0-48 hours was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of RLXL030: actual concentrations at steady state (C_{ss})

End point title	Pharmacokinetics of RLXL030: actual concentrations at steady state (C _{ss}) ^[5]
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End point description:

Concentration at steady state (C_{ss}) was estimated using C48 or C24 for patients who received the intended rate of infusion for at least 24hours. n: Number of patients with valid PK parameters available

End point type	Secondary
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End point timeframe:

pre-infusion and 24, 48 hours post each infusion

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK gets measured on study drug, not on placebo

End point values	RLX030 (serelaxin)			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: ng/ml				
arithmetic mean (standard deviation)				
First infusion (n=174)	31.6 (± 70.1)			
Second Infusion (n=174)	53.5 (± 234)			
Third (n = 181)	38.9 (± 95.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of RLX030: Cmax steady state (Cmaxss) concentration at 48 hours

End point title	Pharmacokinetics of RLX030: Cmax steady state (Cmaxss) concentration at 48 hours ^[6]
End point description:	This analysis was not done due to sparse PK sampling.
End point type	Secondary
End point timeframe:	48 hours post each infusion

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK gets measured on study drug, not on placebo

End point values	RLX030 (serelaxin)			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[7] - This analysis was not done due to sparse PK sampling.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of RLX030: clearance of serelaxin (CL)

End point title	Pharmacokinetics of RLX030: clearance of serelaxin (CL) ^[8]
End point description:	Clearance (CL) was calculated using concentration at steady state (Css) and the actual delivered dose rate. n: Number of patients with valid PK parameters available within 48 hours post each infusion.
End point type	Secondary
End point timeframe:	48 hours post each infusion

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK gets measured on study drug, not on placebo

End point values	RLX030 (serelaxin)			
Subject group type	Reporting group			
Number of subjects analysed	211			
Units: mL/hr/kg				
arithmetic mean (standard deviation)				
First Infusion (n= 173)	106 (± 55.8)			
Second Infusion (n=173)	97.4 (± 41.4)			
Third Infusion (n= 180)	202 (± 1290)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Reporting group title	Serelaxin
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Reporting group description:

Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8

Serious adverse events	Placebo	Serelaxin	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 108 (13.89%)	30 / 212 (14.15%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPOTENSION			

subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE EMERGENCY			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (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			
MEDICAL DEVICE SITE PAIN			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
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			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			

subjects affected / exposed	0 / 108 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 108 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ALCOHOL POISONING			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 108 (0.93%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	2 / 108 (1.85%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	1 / 108 (0.93%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 108 (0.93%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
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 / 108 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			

subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 108 (0.93%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SYNCOPE			
subjects affected / exposed	0 / 108 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAROTID ARTERY STENOSIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD PARALYSIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (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 / 108 (0.93%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 108 (0.93%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDRONEPHROSIS			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
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			
OSTEOARTHRITIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (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			
DIARRHOEA INFECTIOUS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPIDIDYMITIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			

subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 108 (0.93%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGRENE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONSILLAR ABSCESS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 108 (0.93%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL SEPSIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			

subjects affected / exposed	0 / 108 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Placebo	Serelaxin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 108 (36.11%)	65 / 212 (30.66%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	5 / 108 (4.63%)	7 / 212 (3.30%)	
occurrences (all)	6	8	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	3 / 108 (2.78%)	9 / 212 (4.25%)	
occurrences (all)	4	10	
DIZZINESS			
subjects affected / exposed	1 / 108 (0.93%)	10 / 212 (4.72%)	
occurrences (all)	1	10	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 108 (1.85%)	6 / 212 (2.83%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
INFUSION SITE EXTRAVASATION			
subjects affected / exposed	1 / 108 (0.93%)	5 / 212 (2.36%)	
occurrences (all)	1	6	
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 108 (2.78%)	4 / 212 (1.89%)	
occurrences (all)	3	4	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 108 (0.93%)	6 / 212 (2.83%)	
occurrences (all)	1	8	
Respiratory, thoracic and mediastinal disorders			

DYSпноEA subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 3	3 / 212 (1.42%) 3	
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 5	3 / 212 (1.42%) 5	
Musculoskeletal and connective tissue disorders MUSCLE SPASMS subjects affected / exposed occurrences (all) BACK PAIN subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 3 4 / 108 (3.70%) 4	4 / 212 (1.89%) 5 1 / 212 (0.47%) 1	
Infections and infestations PNEUMONIA subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) BRONCHITIS subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 3 8 / 108 (7.41%) 8 4 / 108 (3.70%) 4	1 / 212 (0.47%) 1 18 / 212 (8.49%) 21 2 / 212 (0.94%) 2	
Metabolism and nutrition disorders HYPOKALAEMIA subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 6	3 / 212 (1.42%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2014	This amendment issued before the study initiation (first patient first visit), introduced the following changes: - Addition of the brand name for the infusion filter - A sentence was added to clarify that the use of other 250 mL infusion bags containing 5% dextrose were permitted -the liver monitoring sections of the protocol were updated to match the program and company standard wording and process
21 March 2014	This amendment issued before the study initiation (first patient first visit), introduced the following change(s): - One exclusion criteria was corrected to indicate that women of child-bearing potential must use highly effective methods of contraception. - A section in the protocol was modified to clarify the various methods utilized to ensure protocol and GCP compliance and the quality/integrity of the sites' data. - Per request of German Health Authority as part of additional safety measures to avoid any potential risk of hypotension with the infusion of serelaxin, particular section of the protocol clarified that an infusion pump, a drip or any other controllable infusion system would be used to ensure a constant infusion rate of serelaxin at 10 mL/hr.
28 July 2014	This amendment issued when less than 20 patients were randomized introduced the following change(s): - One exclusion criteria was modified with following sentence "The exception to this exclusion criteria are the low potency topical corticosteroids and inhaled glucocorticoids used for anti-inflammatory effect, e.g. asthma, contact dermatitis, etc". The rationale for allowing low potency topical corticosteroids and inhaled glucocorticoids used for antiinflammatory effects was that these products had no known or negligible systemic effects if used in accordance to approved dosing and in line with medical recommendation. Since the immunomodulating/immunosuppressive actions were minimal and were not expected to affect the objectives of this study, patients requiring such treatment could be enrolled into the study as long as all other inclusion and exclusion criteria have been fulfilled. - One exclusion criteria was modified by adding 'Visit 2' for clarity. - Tables and appendices were updated and modified for clarity.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> for complete trial results.

Notes:

