Clinical trial results:
Multicenter, open-label, dose escalation study to evaluate safety, tolerability and pharmacokinetics of RLX030 in addition to standard of care in pediatric patients from birth to <18 years of age, hospitalized with acute heart failure

Summary

EudraCT number	2013-002847-28
Trial protocol	DE
Global end of trial date	03 April 2017

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	CRLX030A2208

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02151383
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001168-PIP01-11
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	03 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

-To evaluate the safety and tolerability of an iv serelaxin infusion in addition to standard of care in hospitalized pediatric patients with AHF
-To investigate the effects of age on the pharmacokinetics of serelaxin given as iv infusion in addition to standard of care in hospitalized pediatric patients with AHF

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	05 September 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	Germany: 4
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	12
EEA total number of subjects	5

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)	2
Children (2-11 years)	5

Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 18 patients were assigned to study treatment. 6 patients were identified with GCP violations; hence, only 12 patients were included in disposition.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Serelaxin: Cohort 1

Arm description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 1, patients in age group of 6 to <18 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was provided as a 1 mg/mL solution in 6 mL vials (with 3.5 mL fill). The required dose (µg/kg) was calculated for each patient at the assigned dose titration level.

Arm title	Serelaxin: Cohort 2

Arm description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 2, patients in age group of 1 to <6 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was provided as a 1 mg/mL solution in 6 mL vials (with 3.5 mL fill). The required dose (µg/kg) was calculated for each patient at the assigned dose titration level.

Arm title	Serelaxin: Cohort 3

Arm description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total

of 48 hours. In Cohort 3, patients in age group of 1 month to <1 year were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. In this cohort, high- dose group was planned to receive twice the number of patients in low-dose group.

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The study drug was provided as a 1 mg/mL solution in 6 mL vials (with 3.5 mL fill). The required dose (µg/kg) was calculated for each patient at the assigned dose titration level.

Number of subjects in period 1	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3
Started	8	3	1
Low-dose	2 [1]	3	1
High-dose	6 [2]	0 [3]	0 [4]
Completed	8	3	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are fix dose titration groups for the cohort where the cohort patients are assigned to either of these 2 groups.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are fix dose titration groups for the cohort where the cohort patients are assigned to either of these 2 groups.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are fix dose titration groups for the cohort where the cohort patients are assigned to either of these 2 groups.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are fix dose titration groups for the cohort where the cohort patients are assigned to either of these 2 groups.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
These 12 patients are in enrolled and safety set which exclude the 6 patients identified with GCP violations	

Reporting group values	Overall Study	Total	
Number of subjects	12	12	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	5	5	
Age Continuous			
Units: Years			
arithmetic mean	8.1		
standard deviation	± 5.17	-	
Gender, Male/Female			
Units: Subjects			
Female	1	1	
Male	11	11	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	7	7	
Unknown or Not Reported	3	3	

End points

End points reporting groups

Reporting group title	Serelaxin: Cohort 1

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 1, patients in age group of 6 to <18 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Reporting group title	Serelaxin: Cohort 2

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 2, patients in age group of 1 to <6 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Reporting group title	Serelaxin: Cohort 3

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 3, patients in age group of 1 month to <1 year were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. In this cohort, high- dose group was planned to receive twice the number of patients in low-dose group.

Primary: Number of patients reported with treatment emergent any adverse events, serious adverse events and death

End point title	Number of patients reported with treatment emergent any adverse events, serious adverse events and death[1]

End point description:

Number of patients with treatment emergent adverse events (including confirmed systolic blood pressure decreases and worsening heart failure), serious adverse events and death is reported.

End point type	Primary

End point timeframe:

through 28 days + 30 days SAE follow up after completion or discontinuation from the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was planned to be tested.

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	1	
Units: Patients				
at least one Adverse Event	6	3	0	
Serious Adverse Event	3	1	0	
Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameter: Css (steady state concentration)

End point title	Pharmacokinetic parameter: Css (steady state concentration)[2]

End point description:

Steady state concentration was planned to be estimated by 16 hour, 32 hour and 48 hour concentration for each dose level.

End point type	Primary

End point timeframe:

at 0, 2, 16, 22, 32, 40, 48 hr. during the infusion, at 0.5, 4, 8 hours post infusion or study drug discontinuation, and on day 28

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was planned to be tested.

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[3] - PK data was considered too limited for a meaningful interpretation

[4] - PK data was considered too limited for a meaningful interpretation

[5] - PK data was considered too limited for a meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic parameter: CL (clearance)

End point title	Pharmacokinetic parameter: CL (clearance)[6]

End point description:

Clearance(CL) was planned to be estimated using steady state concentration (Css) and rate of infusion.

End point type	Primary

End point timeframe:

at 0, 2, 16, 22, 32, 40, 48 hr. during the infusion, at 0.5, 4, 8 hours post infusion or study drug discontinuation, and on day 28

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was planned to be tested.

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: mL/hr				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[7] - PK data was considered too limited for a meaningful interpretation

[8] - PK data was considered too limited for a meaningful interpretation

[9] - PK data was considered too limited for a meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of arterial blood pressure

End point title	Change from baseline of arterial blood pressure

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: mmHg				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[10] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[11] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[12] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of central venous pressure (CVP)

End point title	Change from baseline of central venous pressure (CVP)

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: mmHg				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[13] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[14] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[15] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of left atrial pressure (LAP)

End point title	Change from baseline of left atrial pressure (LAP)

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[16]	0[17]	0[18]	
Units: mmHg				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[16] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[17] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[18] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of pulmonary artery pressure (PAP– systolic and diastolic)

End point title	Change from baseline of pulmonary artery pressure (PAP– systolic and diastolic)

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: mmHg				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[19] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[20] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[21] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of central venous and arterial oxygen saturation

End point title	Change from baseline of central venous and arterial oxygen saturation

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: percentage				
number (not applicable)				

Notes:

[22] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[23] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[24] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of urine output

End point title	Change from baseline of urine output

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	0[26]	0[27]	
Units: ml/kg/hour				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[25] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[26] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[27] - Data analysis was not done as limited set of data would preclude meaningful interpretation

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of blood lactate levels

End point title	Change from baseline of blood lactate levels

End point description:

End point type	Secondary

End point timeframe:

baseline, prior to each dose escalation, and at 24 hr. post end of infusion

End point values	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: mmol/L				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[28] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[29] - Data analysis was not done as limited set of data would preclude meaningful interpretation

[30] - Data analysis was not done as limited set of data would preclude meaningful interpretation

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Serelaxin: Cohort 1

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 1, patients in age group of 6 to <18 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Reporting group title	Serelaxin: Cohort 2

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 2, patients in age group of 1 to <6 years were enrolled either into a low-dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. Both the low-dose and high- dose groups were planned to receive equal number of patients.

Reporting group title	Serelaxin: Cohort 3

Reporting group description:

Serelaxin was administered intravenously on top of standard therapy for acute heart failure, for a total of 48 hours. In Cohort 3, patients in age group of 1 month to <1 year were enrolled either into a low dose or a high-dose group. During this 48-hour treatment period, the serelaxin dose rates to be administered were 3 µg/kg/day, 10 µg/kg/day and 30 µg/kg/day in the low -dose group; 10 µg/kg/day, 30 µg/kg/day and 100 µg/kg/day in the high-dose group. In this cohort, high- dose group was planned to receive twice the number of patients in low-dose group.

Serious adverse events	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	1 / 3 (33.33%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Serelaxin: Cohort 1	Serelaxin: Cohort 2	Serelaxin: Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	3 / 3 (100.00%)	0 / 1 (0.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure systolic decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Cardioactive drug level increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Ventricular tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 8 (25.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Skin oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Pneumonia viral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hypochloraemia			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2014	No patients had entered this study at the time of this amendment. Health Authority review of the original protocol resulted in study design changes regarding the starting dose (low dose group was added) and the patient sample size. Additional analyses were added with regard to vital signs and adverse events. Feedback from pediatric cardiology experts led to small changes to the exclusion criteria and clarification regarding the criteria for inclusion of patients with a chest x-ray done as part of their standard-of-care.
20 August 2014	No patients had entered the study at the time this amendment was prepared. This amendment mainly described the sub-study regarding additional data collection that was to be conducted in a small number of participating study sites (1-2 sites), which would enable a more in depth exploration of serelaxin's PK-PD relationship
30 September 2016	Fourteen patients had been enrolled in the study at the time this amendment was prepared. The protocol was amended to incorporate changes to enhance the recruitment feasibility for the study without compromising the study objectives or patient safety.

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 the early termination of the study, the planned analyses were not performed as the limited set of data would preclude meaningful interpretation.

Notes: