



Clinical trial results:

A multicenter, randomized, double-blind, crossover placebo-controlled Phase II study to assess the effect of serelaxin versus placebo on high sensitivity cardiac troponin I (hs-cTnI) release in patients with chronic heart failure after exercise when used in addition to standard of care

Summary

EudraCT number	2015-002673-38
Trial protocol	GB DE
Global end of trial date	11 January 2017

Results information

Result version number	v1 (current)
This version publication date	27 January 2018
First version publication date	27 January 2018

Trial information

Trial identification

Sponsor protocol code	CRLX030A2211
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02625922
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	11 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of short-term i.v. administration of serelaxin in CHF patients on the geometric mean of high-sensitivity cardiac troponin I (hs-cTnI) concentrations compared to placebo (both in addition to the standard of care) after an exercise testing session.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2016
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	United Kingdom: 13
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	26
EEA total number of subjects	21

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)	4

From 65 to 84 years	21
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

26 subjects were randomized in 11 study sites from 3 countries (Germany, Switzerland, and the United Kingdom).

Pre-assignment

Screening details:

Patient selection was to be established by checking through all inclusion/exclusion criteria at screening and randomization.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Serelaxin-Placebo

Arm description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

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

Dosage and administration details:

Serelaxin will be administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo i.v infusion.

Arm title	Placebo-Serelaxin
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Arm description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

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

Dosage and administration details:

Matching placebo i.v infusion.

Investigational medicinal product name	Serelaxin
Investigational medicinal product code	
Other name	RLX030
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Serelaxin will be administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

Number of subjects in period 1	Serelaxin-Placebo	Placebo-Serelaxin
Started	14	12
Completed	12	10
Not completed	2	2
Non-availability of IMP	1	1
Systolic blood pressure < 125 mmHg	1	1

Baseline characteristics

Reporting groups

Reporting group title	Serelaxin-Placebo
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Reporting group description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

Reporting group title	Placebo-Serelaxin
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Reporting group description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

Reporting group values	Serelaxin-Placebo	Placebo-Serelaxin	Total
Number of subjects	14	12	26
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)	1	3	4
From 65-84 years	12	9	21
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	74.7	66.5	
standard deviation	± 7.62	± 13.89	-
Gender categorical			
Units: Subjects			
Female	1	2	3
Male	13	10	23

End points

End points reporting groups

Reporting group title	Serelaxin-Placebo
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Reporting group description:

Subjects received serelaxin in Treatment Period 1 and placebo in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

Reporting group title	Placebo-Serelaxin
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Reporting group description:

Subjects received placebo in Treatment Period 1 and serelaxin in Treatment Period 2. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen. Matching placebo was administered as an i.v infusion.

Subject analysis set title	Serelaxin
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants receiving serelaxin in Treatment Period 1 and in Treatment Period 2. Each participant received each of the treatments in randomized order in 2 treatment periods separated by a 15 +/- 1-day washout. Serelaxin was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

Subject analysis set title	Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Participants receiving placebo in Treatment Period 1 and in Treatment Period 2. Each participant received each of the treatments in randomized order in 2 treatment periods separated by a 15 +/- 1-day washout. Placebo was administered as a continuous i.v. infusion according to a weight-range adjusted dosing regimen.

Primary: Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentration After Exercise Compared to Placebo

End point title	Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentration After Exercise Compared to Placebo ^[1]
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End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

End point type	Primary
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End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15+/- 1)

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: The primary analysis of mixed model repeated measures was not performed because the validation of the primary endpoint variable hs-cTnI assay (Singulex Erenna®) was not completed because of the early termination of the study and, therefore, hs-cTnI was not analyzed.

End point values	Serelaxin- Placebo	Placebo- Serelaxin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Overall Number of Participants Analyzed				

Notes:

[2] - Primary endpoint variable hs-cTnI assay was not completed due to the early termination of the study.

[3] - Primary endpoint variable hs-cTnI assay was not completed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentrations After Exercise Compared to Placebo at 4 and 5 Hours

End point title	Geometric Mean of High Sensitivity Cardiac Troponin I (Hs-cTnI) Concentrations After Exercise Compared to Placebo at 4 and 5 Hours
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End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

End point type	Secondary
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End point timeframe:

4 and 5 hours after exercise testing session

End point values	Serelaxin- Placebo	Placebo- Serelaxin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: Overall Number of Participants Analyzed				

Notes:

[4] - Endpoint variable hs-cTnI assay was not analyzed due to the early termination of the study.

[5] - Endpoint variable hs-cTnI assay was not analyzed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Log-transformed Concentration of N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP) Concentrations Compared to Placebo

End point title	Log-transformed Concentration of N-terminal Pro-B-type Natriuretic Peptide (NT-proBNP) Concentrations Compared to Placebo
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End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

End point type	Secondary
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End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15 +/- 1)

End point values	Serelaxin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[6]	26 ^[7]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Baseline	13.5026 (± 0.64893)	13.6217 (± 0.60192)		
132 minutes	13.5729 (± 0.62057)	13.7076 (± 0.61612)		
180 minutes	15.5302 (± 0.62107)	13.6777 (± 0.61118)		
240 minutes	13.5673 (± 0.68419)	13.7011 (± 0.58471)		
300 minutes	13.6103 (± 0.63614)	13.7129 (± 0.57832)		
360 minutes	13.6687 (± 0.65735)	13.7213 (± 0.57366)		
420 minutes	16.6533 (± 0.64776)	13.7399 (± 0.57361)		

Notes:

[6] - The full analysis set (FAS) consisted of all randomized patients.

[7] - The full analysis set (FAS) consisted of all randomized patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Log-transformed Concentration Values of Heart-type Fatty Acid-binding Protein (H-FABP) Concentrations Compared to Placebo

End point title	Log-transformed Concentration Values of Heart-type Fatty Acid-binding Protein (H-FABP) Concentrations Compared to Placebo
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End point description:

This cardiac biomarker measurement was obtained to determine plasma concentrations following a cardiac stress test.

End point type	Secondary
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End point timeframe:

Baseline, up to 7 hours after the start of an exercise testing session on treatment period 1 (Day 1) and treatment period 2 (Day 15 +/- 1).

End point values	Serelaxin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[8]	26 ^[9]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	8.8256 (± 0.67027)	8.8810 (± 0.64372)		
132 minutes	8.8644 (± 0.63646)	8.8409 (± 0.67261)		

180 minutes	8.7897 ($\pm$ 0.62835)	8.7955 ($\pm$ 0.62729)		
240 minutes	8.7718 ($\pm$ 0.63971)	8.8662 ($\pm$ 0.58565)		
300 minutes	8.7309 ($\pm$ 0.62177)	8.7202 ($\pm$ 0.65890)		
360 minutes	8.7692 ($\pm$ 0.64920)	8.8088 ($\pm$ 0.59672)		
420 minutes	8.7669 ($\pm$ 0.65793)	8.7329 ($\pm$ 0.63139)		

Notes:

[8] - The full analysis set (FAS) consisted of all randomized patients.

[9] - The full analysis set (FAS) consisted of all randomized patients.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are monitored from on or after the time of first administration of study treatment up to 30 days after the last administration were included.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Serelaxin
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Reporting group description:

Serelaxin

Reporting group title	Total
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Reporting group description:

Total

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	Serelaxin	Total	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Serelaxin	Total	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	12 / 22 (54.55%)	6 / 20 (30.00%)
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	2 / 22 (9.09%) 2	0 / 20 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	1 / 20 (5.00%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	1 / 20 (5.00%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	1 / 20 (5.00%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	1 / 20 (5.00%) 1
Renal and urinary disorders			

Urinary retention subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 22 (4.55%) 1	1 / 20 (5.00%) 1
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0
Infections and infestations Rhinitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 22 (4.55%) 1	0 / 20 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2015	- Updated the assessment of pregnancy according to new information from preclinical studies and the updated Investigator's Brochure. An additional time point for the pregnancy test was included - Updated the list of exclusion criteria. Exclusion criterion 2 was removed because the patient population was defined as stable based on inclusion criterion 3 and exclusion criterion 6 - Clarified that the Data Monitoring Committee could not terminate the study independently, but could only issue a recommendation to the Sponsor - Provided clarification on the reporting of AEs during the study - Improved the clarity of the description and graphic representation of the Borg CR10 scale and the echocardiography
20 December 2016	- Adjusted inclusion criterion 4 and defined left ventricular ejection fraction < 50% according to the updated heart failure guidelines of the European Society of Cardiology - Adjusted inclusion criterion 5 to NT-proBNP > 250 ng/L - Adjusted exclusion criterion 14 to exclude patients with a history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy less than 1 year - Removed exclusion criterion 4 and accounted for the fact that the primary purpose of the Screening exercise test was to calculate a workload that would stress the patient but allowed them to complete the 12-minute exercise at Treatment Periods 1 and 2. Therefore, maximum capacity threshold of $VCO_2/VO_2 > 1.05$ was not to be an exclusion criterion per se - Updated exclusion criterion 17 to match the description of highly effective contraception methods in the current template

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.

The study was terminated early by Novartis, 19-Apr-2017. Because of the early termination of the study, the validation of the hs-cTnI assay was not completed and the primary efficacy endpoint was not analyzed.

Notes: