



Clinical trial results:

A randomized, subject and investigator-blind, placebo controlled study of CLR325 in chronic stable heart failure patients

Summary

EudraCT number	2016-001387-12
Trial protocol	DE BE NL
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	CCLR325X2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02696967
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)	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	14 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the safety and tolerability of an 18-hour i.v. infusion of CLR325 in patients with stable heart failure

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	17 May 2016
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: 3
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	26
EEA total number of subjects	6

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)	21
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 11 centers in 5 countries: Belgium (1), Germany (2), Netherlands (1), Singapore (1) and USA (6).

Pre-assignment

Screening details:

Patients were assigned to one of the 2 treatment arms in fixed randomization ratio (CLR325: Placebo):

- Cohort 1: Single dose of CLR325 2.5 µg/kg/min (i.v.) or placebo (i.v.)
- Cohort 2: Single dose of CLR325 0.25 µg/kg/min (i.v.) or placebo (i.v.)
- Cohort 3: Single dose of CLR325 8 µg/kg/min (i.v.) or placebo (i.v.)

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CLR325 0.25 mcg/kg/min

Arm description:

Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.

Arm type	Experimental
Investigational medicinal product name	CLR325
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CLR325 120 mg/10 mL (liquid in vial)

Arm title	CLR325 2.5 mcg/kg/min
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Arm description:

Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.

Arm type	Experimental
Investigational medicinal product name	CLR325
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CLR325 120 mg/10 mL (liquid in vial)

Arm title	CLR325 8 mcg/kg/min
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Arm description:

Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.

Arm type	Experimental
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Investigational medicinal product name	CLR325
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: CLR325 120 mg/10 mL (liquid in vial)	
Arm title	Placebo

Arm description:

Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo to CLR325 120mg/10mL

Number of subjects in period 1	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Started	4	6	6
Pharmacokinetic (PK) analysis set	4	6	4 ^[1]
Completed	4	6	6

Number of subjects in period 1	Placebo
Started	10
Pharmacokinetic (PK) analysis set	0 ^[2]
Completed	10

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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

[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: Pharmacokinetic sampling only performed on CLR325 treatment arms (does not apply to placebo randomized patients)

Baseline characteristics

Reporting groups

Reporting group title	CLR325 0.25 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	CLR325 2.5 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	CLR325 8 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	Placebo
Reporting group description: Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.	

Reporting group values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Number of subjects	4	6	6
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)	4	5	3
From 65-84 years	0	1	3
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	56.5	55.2	63.5
standard deviation	± 3.1	± 13.0	± 11.8
Sex: Female, Male Units: Subjects			
Female	1	0	2
Male	3	6	4
Race/Ethnicity, Customized Units: Subjects			
Caucasian	4	3	4
Black	0	2	2
Asian	0	1	0

Reporting group values	Placebo	Total	
Number of subjects	10	26	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	21	
From 65-84 years	1	5	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	54.2		
standard deviation	± 9.2	-	
Sex: Female, Male Units: Subjects			
Female	0	3	
Male	10	23	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	8	19	
Black	1	5	
Asian	1	2	

End points

End points reporting groups

Reporting group title	CLR325 0.25 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	CLR325 2.5 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	CLR325 8 mcg/kg/min
Reporting group description: Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	
Reporting group title	Placebo
Reporting group description: Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.	

Primary: Number of patients with adverse events, serious adverse events and death

End point title	Number of patients with adverse events, serious adverse events and death ^[1]
End point description: Analysis of absolute and relative frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC) in each treatment arm to demonstrate that CLR325 is safe for the treatment of chronic stable heart-failure patients through the monitoring of relevant clinical and laboratory safety parameters.	
End point type	Primary
End point timeframe: Day 1 to 28	
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: Only descriptive analysis performed	

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	6	10
Units: Participants				
On-treatment Adverse Event (AEs)	1	3	4	7
On-treatment Serious Adverse Event (SAEs)	0	2	2	0
On-treatment Deaths	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to 18 hours (AUC0-18hr)

End point title	Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to 18 hours (AUC0-18hr) ^[2]
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End point description:

AUC0-18hr is the area under the plasma concentration-time curve from time zero to 18 hours after the start of CLR325 infusion. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0, 0.5, 3, 5, 8, 10, 12, and 18 hours post start of CLR325 infusion on Day 1

Notes:

[2] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
CLR 325	1220 (± 10.4)	18500 (± 31.6)	79700 (± 32.5)	
CQJ295	999 (± 999)	623 (± 102.3)	5560 (± 46.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from from time zero to 28 hours (AUC0-28hrs)

End point title	Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from from time zero to 28 hours (AUC0-28hrs) ^[3]
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End point description:

AUC0-28hr is the area under the plasma concentration-time curve from time zero to 28 hours after the start of CLR325 infusion. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1

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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
CLR325	1460 (± 12.8)	21500 (± 32.9)	100000 (± 28.2)	
CQJ295	999 (± 999)	838 (± 106.2)	8390 (± 43.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to infinity (AUCinf)

End point title	Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to infinity (AUCinf) ^[4]
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End point description:

AUCinf is the area under the plasma concentration-time curve from time zero to infinity. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1

Notes:

[4] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
CLR325	1510 (± 4.7)	21900 (± 34.0)	103000 (± 26.1)	
CQJ295	999 (± 999)	843 (± 49.9)	9660 (± 38.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUClast)

End point title	Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUClast) ^[5]
End point description: AUClast is the area under the plasma concentration-time curve from time zero to the last measurable concentration sampling time. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.	
End point type	Secondary
End point timeframe: 0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1	

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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
CLR325	1450 (± 13.0)	21500 (± 32.9)	100000 (± 28.2)	
CQJ295	3.10 (± 999)	836 (± 107.1)	8380 (± 43.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325: clearance from plasma (CL) following drug administration

End point title	Pharmacokinetic of CLR325: clearance from plasma (CL) following drug administration ^[6]
End point description: CL is the systemic (or total body) clearance from plasma following CLR325 infusion. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.	
End point type	Secondary
End point timeframe: 0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1	

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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: mL/hr				
geometric mean (geometric coefficient of variation)	15200 (± 6.1)	13200 (± 54.9)	7460 (± 15.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: observed maximum plasma concentration following drug administration at steady state (C_{max,ss})

End point title	Pharmacokinetic of CLR325 and CQJ295: observed maximum plasma concentration following drug administration at steady state (C _{max,ss}) ^[7]
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End point description:

C_{max,ss} is the observed maximum plasma concentration following drug administration at steady state. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1

Notes:

[7] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
CLR325	103 (± 11.2)	1370 (± 36.0)	6080 (± 38.4)	
CQJ295	999 (± 999)	54.2 (± 91.0)	468 (± 54.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: terminal elimination half-life (T_{1/2})

End point title	Pharmacokinetic of CLR325 and CQJ295: terminal elimination half-life (T _{1/2}) ^[8]
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End point description:

T_{1/2} is the elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve. PK parameters were calculated from plasma concentration-time data using non-

compartmental methods. Only descriptive analysis performed.

End point type	Secondary
End point timeframe:	
18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1	

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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: hr				
arithmetic mean (standard deviation)				
CLR325	1.86 (± 0.197)	2.99 (± 0.520)	2.96 (± 0.992)	
CQJ295	999 (± 999)	3.12 (± 0.275)	5.73 (± 3.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: time to reach the maximum concentration after drug administration (TMax)

End point title	Pharmacokinetic of CLR325 and CQJ295: time to reach the maximum concentration after drug administration (TMax) ^[9]
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End point description:

Tmax is the time to reach maximum plasma concentration after single dose administration. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
End point timeframe:	
0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1	

Notes:

[9] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: hr				
median (full range (min-max))				
CLR325	14.0 (4.93 to 18.0)	12.0 (8.05 to 12.1)	14.9 (8.08 to 17.9)	
CQJ295	0 (0 to 5.03)	15.1 (7.92 to 18.1)	17.9 (8.33 to 18.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325: volume of distribution at steady state following intravenous administration (Vss)

End point title	Pharmacokinetic of CLR325: volume of distribution at steady state following intravenous administration (Vss) ^[10]
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End point description:

Vss is the volume of distribution at steady state following intravenous administration. PK parameters were calculated from plasma concentration-time data using non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0, 0.5, 3, 5, 8, 10, 12, 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1

Notes:

[10] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: mL				
geometric mean (geometric coefficient of variation)	51600 (± 19.6)	32500 (± 47.6)	28000 (± 33.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: Amount of drug (or defined metabolite) excreted into the urine from time (Ae 0-28 hours)

End point title	Pharmacokinetic of CLR325 and CQJ295: Amount of drug (or defined metabolite) excreted into the urine from time (Ae 0-28 hours) ^[11]
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End point description:

Ae 0-28 hours is the amount of drug (or defined metabolite) excreted into the urine from time zero to 28 hours after the start of CLR325 infusion. The urine PK parameters were measured using a non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0-28 hours on Day 1

Notes:

[11] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: ng				
geometric mean (geometric coefficient of variation)				
CLR325	999 (± 999)	19500000 (± 125.2)	41300000 (± 253.3)	
CQJ295	999 (± 999)	7620000 (± 27.2)	4040000 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic of CLR325 and CQJ295: renal clearance from plasma (CLr) following drug administration

End point title	Pharmacokinetic of CLR325 and CQJ295: renal clearance from plasma (CLr) following drug administration ^[12]
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End point description:

CLr is the renal clearance from urine following CLR325 infusion. The urine PK parameters were measured using an non-compartmental methods. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

0-28 hours on Day 1

Notes:

[12] - 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: Pharmacokinetic (PK) analysis set = At least one dose of study drug and one evaluable PK concentration measurement

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: mL/hr				
geometric mean (geometric coefficient of variation)				
CLR325	999 (± 999)	904 (± 199.4)	411 (± 395.1)	
CQJ295	999 (± 999)	5620 (± 71.7)	258 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with increase in anti-CLR325 and anti-apelin antibodies in serum

End point title	Number of patients with increase in anti-CLR325 and anti-apelin antibodies in serum
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End point description:

Anti-CLR325 anti-apelin antibodies in serum were analyzed predose, Day 10 and Day 28 to determine the immunogenicity of an 18-hour i.v. infusion of CLR325 in heart failure patients.

End point type	Secondary
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End point timeframe:

Baseline, Day 10 and Day 28

End point values	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	6	10
Units: Participants				
BL anti-Apelin antibody Antibody detected = Yes	0	0	0	0
BL anti-CLR325 antibody Antibody detected = Yes	0	0	0	0
D10 anti-Apelin antibody Antibody detected = Yes	0	0	0	0
D10 anti-CLR325 antibody Antibody detected = Yes	0	0	0	0
D28 anti-Apelin antibody Antibody detected = Yes	0	0	0	0
D28 anti-CLR325 antibody Antibody detected = Yes	0	0	0	0
BL anti-Apelin antibody Antibody detected = No	1	1	1	0
BL anti-CLR325 antibody Antibody detected = No	4	5	5	10
D10 anti-Apelin antibody Antibody detected = No	0	0	1	1
D10 anti-CLR325 antibody Antibody detected = No	3	4	6	7
D28 anti-Apelin antibody Antibody detected = No	1	0	1	0
D28 anti-CLR325 antibody Antibody detected = No	3	5	5	9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from first dose of study treatment until end of study treatment plus 30 days post-treatment, up to maximum duration of 1 month.

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	21.1
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Reporting groups

Reporting group title	CLR325 0.25 mcg/kg/min
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Reporting group description:

Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.

Reporting group title	CLR325 2.5 mcg/kg/min
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Reporting group description:

Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.

Reporting group title	CLR325 8 mcg/kg/min
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Reporting group description:

Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.

Reporting group title	Placebo
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Reporting group description:

Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.

Serious adverse events	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	4 / 6 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Generalised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infusion site pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory tract congestion			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Investigations			
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Liver function test increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Pulmonary arterial wedge pressure decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Injury, poisoning and procedural complications			
Muscle strain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Procedural pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 3
Cardiogenic shock subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Ventricular tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	2 / 6 (33.33%) 2

Headache subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Blood and lymphatic system disorders Haemorrhagic anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Ileus subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1	1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1
Skin and subcutaneous tissue disorders Cold sweat subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 6 (0.00%) 0 1 / 6 (16.67%) 1
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Azotaemia subjects affected / exposed occurrences (all) Haematuria	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	1 / 6 (16.67%) 1 1 / 6 (16.67%) 1

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infusion site pruritus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory tract congestion			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Liver function test increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Pulmonary arterial wedge pressure decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Injury, poisoning and procedural complications Muscle strain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Procedural pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Cardiogenic shock subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Ventricular tachycardia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		

Headache subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Blood and lymphatic system disorders Haemorrhagic anaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Ileus subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Cold sweat subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Azotaemia subjects affected / exposed occurrences (all) Haematuria	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		

subjects affected / exposed occurrences (all) Urinary retention subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2016	Amendment 1 was issued to: • To reduce patient burden and improve patient safety, the measurement of right ventricular pressures using the pulmonary artery catheter was made optional. • To reduce patient burden, non-invasive hemodynamic monitoring was made optional at select sites. This will reduce the number of electrodes on the patient's chest and improve overall patient comfort during the study. • To reduce patient burden, the screening period has been expanded to Day 1 to allow a patient to be screened and enrolled in the study in the same day, reducing the need for multiple patient visits to the site to participate in this study.
05 August 2016	Amendment 2: • The primary purpose of this amendment was to enhance patient safety in response to a suspected, unexpected, SAE (occurred in a subject who experienced a rise in liver function tests during infusion of study drug that reversed without intervention following termination of the infusion). The etiology of this event could be related to prior underlying liver disease or to a volume-depleted state (as indicated by a low PCWP at baseline) in this subject. An exclusion criterion was added to exclude patients with underlying liver disease or with relative volume depletion. • This protocol amendment also clarified criteria around pulse rate and anticoagulation management and monitoring of coagulation laboratories as requested by BfArM.
07 February 2017	Amendment 3: • The primary purpose of this protocol amendment is to reduce patient burden by establishing additional cohorts that utilized echocardiography rather than invasive hemodynamics to monitor changes in cardiac index during infusion of study medication. This allowed chronic stable heart failure patients to be enrolled in this study without the placement of a pulmonary artery catheter, thus reducing the risk to patients from catheter-related complications (e.g., bleeding, arrhythmias). The number of additional cohorts that can be recruited in this study was increased from 3 to 4 and the randomization ratio is modified to 1:1 for all additional cohorts to increase power to detect changes in hemodynamics during study drug infusion.
31 October 2017	Amendment 4: • Experience from the first cohort (n = 8) of patients with chronic stable heart failure treated with CLR325 indicated that CLR325 was generally well tolerated. The AEs were few and balanced between CLR325 and placebo treated patients. Given this acceptable safety profile with CLR325 in chronic stable heart failure patients, the inclusion and exclusion criteria was modified to allow the recruitment of stabilized, acutely decompensated heart failure patients. As such, these patients would be a population, which more closely reflects the target population for the development of CLR325 as a novel cardiac inotrope. • The protocol also clarified regarding the exclusion criteria on echocardiographic assessment of volume status (exclusion criteria #17). This criterion was included to exclude those patients with low PCWP (<10 mm Hg) as described in Amendment 2.
27 August 2018	Amendment 5: • Based on a review of the data, this amendment was designed to reduce patient and site burden by eliminating the requirement to obtain thermodilution cardiac outputs. Elimination of thermodilution cardiac outputs reduced the volume load given to each patient during the course of the study. Finally, removal of thermodilution cardiac outputs also reduced burden on the sites, as these determinations are very labor intensive. • The screening window was expanded, updated withdrawal of consent language, and clarified criteria for laboratory tests, replacement patients, and urine PK collection to improve site operations.

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.nov for complete trial results.
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Notes: