NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

CLR325

Trial Indication(s)

Chronic stable heart failure

Protocol Number

CCLR325X2202

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IIa

Study Start/End Dates

Study Start Date: May 2016 (Actual)
Primary Completion Date: January 2019 (Actual)
Study Completion Date: January 2019 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This is a non-confirmatory, randomized, subject and investigator-blind, placebo-controlled study of an 18-h i.v. infusion of CLR325 in patients with stable heart failure (who could have a clinically indicated pulmonary artery (PA) catheter in place) to assess safety, tolerability, and PK in this patient population. Cohort 1 (2.5 µg/kg/min) enrolled 8 patients with chronic stable heart failure (patients with a PA catheter) in a 3:1 ratio (CLR325: placebo). Cohort 2 (0.25 µg/kg/min) enrolled 8 patients with chronic stable heart failure in a 1:1 ratio and used echocardiography to monitor cardiac hemodynamics. Subsequently, Cohort 3 (8 µg/kg/min) enrolled 10 patients with either acute decompensation and chronic stable heart failure (patients with a PA catheter) in a 1:1 ratio (CLR325: placebo). Stratified randomization was used with 'heart failure type' as a stratification factor (chronic vs. stabilized acutely decompensated).

Centers

12 centers in 5 countries: United States(7), Singapore(1), Germany(2), Netherlands(1), Belgium(1)

Objectives:

Primary objective: To determine the safety and tolerability of an 18-hour i.v. infusion of CLR325 in patients with stable heart failure

Secondary objectives:

- To determine the pharmacokinetics (PK) of CLR325, and the active metabolite, CQJ295, during an 18-h i.v. infusion of CLR325 in heart failure patients
- To determine the immunogenicity of an 18-h i.v. infusion of CLR325 in heart failure patients

Test Product (s), Dose(s), and Mode(s) of Administration

CLR325 120 mg/10 mL (liquid in vial) was used in the study. Normal saline was used as placebo, which was procured locally by the sites.

Statistical Methods

CLR325 plasma concentration data were listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics was provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
• Male and female patients >18 years of age
• Body weight between 50 kg and 140 kg
• Cardiac ejection fraction of ≤ 45% assessed within the last 6 months
• For PA catheter cohorts, patients who are planned to have a clinically indicated pulmonary artery catheter in place prior to randomization
• In the opinion of the investigator, heart failure patients who do not require a change in their dose of acetylcholinesterase (ACE), angiotensin receptor blocker (ARB), β-blocker, mineralocorticoid receptor antagonist, or diuretic for 24 h after randomization.
• At Baseline, vital signs (systolic and diastolic blood pressure and pulse rate) assessment in the supine position after the subject has rested for at least five minutes.

Key Exclusion Criteria:
• Impaired renal function as indicated by clinically significant abnormal creatinine values (Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 calculated using the Modification of Diet in Renal Disease Study (MDRD) equation)
• History of chronic hepatitis of any non-cardiac etiology
• History of any active or clinically significant cardiac tachyarrhythmia (such as recurrent atrial fibrillation with rapid ventricular response within the last year) and patients with chronic atrial fibrillation with a pulse rate ≤ 100 bpm
• Patients who received an i.v. infusion of a cardiac inotrope (e.g., dobutamine or milrinone) in the last 24 h prior to randomization
• Patients with any significant change in their dose of their ACE, ARB, mineralocorticoid receptor antagonist, diuretic, or β-blocker within the last 12 h
• Patients with known significant valvular heart diseases indicated by the following:
° severe aortic stenosis (aortic valve area < 1.0 cm2 or peak gradient > 50 mm Hg as determined by echocardiography)
° severe mitral stenosis
• History of acute coronary syndrome within the last 60 days as determined by both clinical and enzymatic criteria
• For echocardiography-based cohorts only, patients admitted to an inpatient setting for acute decompensated heart failure within the last 30 days

• For PA catheter cohorts, patients with a pulmonary capillary wedge pressure of <10 mm Hg at Baseline. For echocardiographic cohorts, patients with a lateral E/E' ratio of < 7 on their baseline echocardiogram. For patients in whom a lateral E/E' ratio cannot be determined (e.g., patients in atrial fibrillation), a central venous pressure of < 5 mm Hg on baseline echocardiogram as determined by inferior vena cava criteria.

Participant Flow Table

Overall Study

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo	Total
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.	
Started	4	6	6	10	26
Pharmacokinetic (PK) analysis set	4	6	4	0	14
Completed	4	6	6	10	26
Not Completed	0	0	0	0	0

Baseline Characteristics

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo	Total
Arm/Group Description	Patients randomized to this arm	Patients randomized to this arm	Patients randomized to this arm	Patients randomized to this arm	

	received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	received single dose of Placebo (i.v.) in double blind manner.	
Number of Participants [units: participants]	4	6	6	10	26
Age Continuous (units: Years) Mean ± Standard Deviation					
	56.5±3.1	55.2±13.0	63.5±11.8	54.2±9.2	56.9±10.4
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)					
Female	1	0	2	0	3
Male	3	6	4	10	23
Race/Ethnicity, Customized (units: Participants)					
Caucasian	4	3	4	8	19
Black	0	2	2	1	5
Asian	0	1	0	1	2

Summary of Efficacy

Primary Outcome Result(s)

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

(Time Frame: Day 1 to 28)

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	6	10
Number of patients with adverse events, serious adverse events and death (units: Participants) Count of Participants (Not Applicable)				
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

Secondary Outcome Result(s)

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

(Time Frame: 0, 0.5, 3, 5, 8, 10, 12, and 18 hours post start of CLR325 infusion on Day 1)

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received	Patients randomized to this arm received	Patients randomized to this arm received

	single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to 18 hours (AUC0-18hr) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR 325	1220 (10.4%)	18500 (31.6%)	79700 (32.5%)
CQJ295	N/A (N/A%)[1]	623 (102.3%)	5560 (46.7%)

[1] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))

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

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

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from from time zero to 28 hours (AUC0-28hrs)			

(units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	1460 (12.8%)	21500 (32.9%)	100000 (28.2%)
CQJ295	N/A (N/A%)[1]	838 (106.2%)	8390 (43.5%)

[1] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))

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

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

	CLR325 0.25 mcg/kg/min	**CLR325 2.5 mcg/kg/min**	**CLR325 8 mcg/kg/min**
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to infinity (AUCinf) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	1510 (4.7%)	21900 (34.0%)	103000 (26.1%)
CQJ295		843 (49.9%)	9660 (38.5%)

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

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

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUClast) (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	1450 (13.0%)	21500 (32.9%)	100000 (28.2%)
CQJ295	3.10 (N/A%)[1]	836 (107.1%)	8380 (43.6%)

[1] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))

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

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

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.

Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325: clearance from plasma (CL) following drug administration (units: mL/hr) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	15200 (6.1%)	13200 (54.9%)	7460 (15.4%)

Pharmacokinetic of CLR325 and CQJ295: observed maximum plasma concentration following drug administration at steady state (Cmax,ss)

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

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: observed maximum plasma concentration following drug administration at steady state (Cmax,ss) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	103 (11.2%)	1370 (36.0%)	6080 (38.4%)
CQJ295	N/A (N/A%)[1]	54.2 (91.0%)	468 (54.0%)

[1] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))

Pharmacokinetic of CLR325 and CQJ295: terminal elimination half-life (T1/2)

(Time Frame: 18, 20, 24, and 28 hours post start of CLR325 infusion on Day 1)

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: terminal elimination half-life (T1/2) (units: hr) Mean ± Standard Deviation			
CLR325	1.86 ± 0.197	2.99 ± 0.520	2.96 ± 0.992
CQJ295		3.12 ± 0.275	5.73 ± 3.38

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

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

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min

	(i.v.) in double blind manner.	(i.v.) in double blind manner.	(i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: time to reach the maximum concentration after drug administration (TMax) (units: hr) Median (Full Range)			
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)

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

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

	CLR325 0.25 mcg/kg/min	**CLR325 2.5 mcg/kg/min**	**CLR325 8 mcg/kg/min**
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325: volume of distribution at steady state following intravenous administration (Vss)			

(units: mL) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	51600 (19.6%)	32500 (47.6%)	28000 (33.3%)

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

(Time Frame: 0-28 hours on Day 1)

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: Amount of drug (or defined metabolite) excreted into the urine from time (Ae 0-28 hours) (units: ng) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	N/A (N/A%)[1]	19500000 (125.2%)	41300000 (253.3%)
CQJ295	N/A (N/A%)[2]	7620000 (27.2%)	4040000 (N/A%)[3]

[1] N/A: Not Estimable (CLR325 concentration below lower limit of quantification (LLOQ))
[2] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))
[3] NA: Not estimable due to insufficient number of participants with events

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

(Time Frame: 0-28 hours on Day 1)

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.
Number of Participants Analyzed [units: participants]	4	6	4
Pharmacokinetic of CLR325 and CQJ295: renal clearance from plasma (CLr) following drug administration (units: mL/hr) Geometric Mean (Geometric Coefficient of Variation)			
CLR325	N/A (N/A%)[1]	904 (199.4%)	411 (395.1%)
CQJ295	N/A (N/A%)[2]	5620 (71.7%)	258 (N/A%)[3]

[1] N/A: Not Estimable (CLR325 concentration below lower limit of quantification (LLOQ))
[2] N/A: Not Estimable (CQJ295 concentration below lower limit of quantification (LLOQ))
[3] NA: Not estimable due to insufficient number of participants with events

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

(Time Frame: Baseline (BL), Day 10 (D10) and Day 28 (D28))

	CLR325 0.25 mcg/kg/min	CLR325 2.5 mcg/kg/min	CLR325 8 mcg/kg/min	Placebo
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.

Number of Participants Analyzed [units: participants]	4	6	6	10
Number of patients with increase in anti-CLR325 and anti-apelin antibodies in serum (units: Participants) Count of Participants (Not Applicable)				
BL anti-Apelin 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 = Yes	0	0	0	0
BL anti-CLR325 antibody : Antibody detected = No	4	5	5	10
D10 anti-Apelin antibody : Antibody detected = Yes	0	0	0	0
D10 anti-Apelin antibody : Antibody detected = No	0	0	1	1
D10 anti-CLR325 antibody : Antibody detected = Yes	0	0	0	0
D10 anti-CLR325 antibody : Antibody detected = No	3	4	6	7
D28 anti-Apelin antibody : Antibody detected = Yes	0	0	0	0
D28 anti-Apelin antibody : Antibody detected = No	1	0	1	0
D28 anti-CLR325 antibody : Antibody detected = Yes	0	0	0	0
D28 anti-CLR325 antibody : Antibody detected = No	3	5	5	9

Summary of Safety

Safety Results

All-Cause Mortality

	CLR325 0.25 mcg/kg/min N = 4	CLR325 2.5 mcg/kg/min N = 6	CLR325 8 mcg/kg/min N = 6	Placebo N = 10
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	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.
Additional Description	All randomized patients received a single i.v. infusion of CLR325 or placebo for approximately 18 hours. Any sign or symptom that occurs during the study treatment and 30 days post-treatment follow up.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	CLR325 0.25 mcg/kg/min N = 4	CLR325 2.5 mcg/kg/min N = 6	CLR325 8 mcg/kg/min N = 6	Placebo N = 10
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.
Total participants affected	0 (0.00%)	2 (33.33%)	2 (33.33%)	0 (0.00%)
Cardiac disorders				
Acute myocardial infarction	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Cardiac failure congestive	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Infections and infestations				
Bronchitis	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)
Investigations				
Hepatic enzyme increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				
Delirium	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	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.
Additional Description	All randomized patients received a single i.v. infusion of CLR325 or placebo for approximately 18 hours. Any sign or symptom that occurs during the study treatment and 30 days post-treatment follow up.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	CLR325 0.25 mcg/kg/min N = 4	**CLR325 2.5 mcg/kg/min N = 6**	**CLR325 8 mcg/kg/min N = 6**	**Placebo N = 10**
Arm/Group Description	Patients randomized to this arm received single dose of CLR325 0.25 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 2.5 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of CLR325 8 mcg/kg/min (i.v.) in double blind manner.	Patients randomized to this arm received single dose of Placebo (i.v.) in double blind manner.
Total participants affected	1 (25.00%)	2 (33.33%)	4 (66.67%)	7 (70.00%)
Blood and lymphatic system disorders				
Haemorrhagic anaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Cardiac disorders				
Angina pectoris	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Cardiogenic shock	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Ventricular tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)

Ear and labyrinth disorders				
Ear discomfort	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Gastrointestinal disorders				
Diarrhoea	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Ileus	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nausea	1 (25.00%)	0 (0.00%)	1 (16.67%)	1 (10.00%)
General disorders and administration site conditions				
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Feeling hot	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Generalised oedema	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Infusion site pruritus	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Infections and infestations				
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Injury, poisoning and procedural complications				
Muscle strain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Investigations				
Haemoglobin decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Liver function test increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)

Pulmonary arterial wedge pressure decreased	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Metabolism and nutrition disorders				
Hypokalaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Haemangioma of liver	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nervous system disorders				
Dizziness	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)
Headache	1 (25.00%)	0 (0.00%)	0 (0.00%)	3 (30.00%)
Renal and urinary disorders				
Acute kidney injury	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Azotaemia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Haematuria	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Urinary retention	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)

Respiratory, thoracic and mediastinal disorders				
Atelectasis	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Epistaxis	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Pleural effusion	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Respiratory tract congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Skin and subcutaneous tissue disorders				
Cold sweat	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Pruritus	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Vascular disorders				
Flushing	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Hypertension	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypotension	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

CLR325 was safe and well tolerated in this study during an 18 hour i.v. infusion. The pharmacokinetics of CLR325 and CQJ295 found in this study is comparable to that from the first in human study in healthy subjects. Anti-CLR325 antibodies were not detected at baseline and after CLR325 administration during the study in any of the patients.

Date of Clinical Trial Report

12-Sep-2019