



Clinical trial results:

A Phase IIa Study of the Safety, Tolerability and Hemodynamic Effects of a Continuous 6-Hour Intravenous Infusion of CXL-1427 in Hospitalized Patients with Systolic Heart Failure

Summary

EudraCT number	2014-000771-24
Trial protocol	DE
Global end of trial date	21 March 2015

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019

Trial information

Trial identification

Sponsor protocol code	CV013-006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Other Identifier: CXL-1427-02

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.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	21 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and tolerability of 6-hour intravenous infusions of CXL-1427 in patients with systolic congestive heart failure. Evaluate the effects of 6-hour intravenous infusions of CXL-1427 on pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure (PAD) and cardiac index (CI), as measured by an indwelling pulmonary artery (PA) catheter

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Jordan: 3
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	70
EEA total number of subjects	9

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)	46
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 70 participants were enrolled of which only 46 participants received treatment. 24 were not treated due to screen failures, 3 of the 24 were randomized but not dosed due to other reasons.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo intravenous (IV) infusion.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo of BMS-986231
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

5% Dextrose & 10mM potassium acetate as same IV solution diluents used in active

Arm title	CXL-1427 3µg/kg/min
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Arm description:

Subjects received CXL-1427 3 microgram per kilogram per minute (µg/kg/min) IV infusion as 90 milliliter (mL) of dosing solution at a rate of 15 milliliter per hour (mL/hour) for six hours.

Arm type	Experimental
Investigational medicinal product name	CXL-1427
Investigational medicinal product code	BMS-986231
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mcg/kg/min

Arm title	CXL-1427 5µg/kg/min
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Arm description:

Subjects received CXL-1427 5 µg/kg/min IV infusion as 90 mL of dosing solution at a rate of 15 mL/hour for six hours.

Arm type	Experimental
Investigational medicinal product name	CXL-1427
Investigational medicinal product code	BMS-986231
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mcg/kg/min

Arm title	CXL-1427 7µg/kg/min
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Arm description:

Subjects received CXL-1427 7 µg/kg/min IV infusion as 150 mL of dosing solution at a rate of 25 mL/hour for six hours.

Arm type	Experimental
Investigational medicinal product name	CXL-1427
Investigational medicinal product code	BMS-986231
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

7 mcg/kg/min

Arm title	CXL-1427 12µg/kg/min
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Arm description:

Subjects received CXL-1427 12 µg/kg/min IV infusion as 180 mL of dosing solution at a rate of 30 mL/hour for six hours.

Arm type	Experimental
Investigational medicinal product name	CXL-1427
Investigational medicinal product code	BMS-986231
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mcg/kg/min

Number of subjects in period 1^[1]	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min
Started	12	6	9
Completed	12	5	8
Not completed	0	1	1
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	-	1

Number of subjects in period 1^[1]	CXL-1427 7µg/kg/min	CXL-1427 12µg/kg/min
Started	12	7
Completed	12	7
Not completed	0	0
Adverse event, non-fatal	-	-
Lost to follow-up	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 70 participants were enrolled worldwide, of which only 46 participants received treatment. Baseline period subject disposition is shown for 46 randomized and treated participants

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received matching placebo intravenous (IV) infusion.	
Reporting group title	CXL-1427 3µg/kg/min
Reporting group description: Subjects received CXL-1427 3 microgram per kilogram per minute (µg/kg/min) IV infusion as 90 milliliter (mL) of dosing solution at a rate of 15 milliliter per hour (mL/hour) for six hours.	
Reporting group title	CXL-1427 5µg/kg/min
Reporting group description: Subjects received CXL-1427 5 µg/kg/min IV infusion as 90 mL of dosing solution at a rate of 15 mL/hour for six hours.	
Reporting group title	CXL-1427 7µg/kg/min
Reporting group description: Subjects received CXL-1427 7 µg/kg/min IV infusion as 150 mL of dosing solution at a rate of 25 mL/hour for six hours.	
Reporting group title	CXL-1427 12µg/kg/min
Reporting group description: Subjects received CXL-1427 12 µg/kg/min IV infusion as 180 mL of dosing solution at a rate of 30 mL/hour for six hours.	

Reporting group values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min
Number of subjects	12	6	9
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)	9	3	6
From 65-84 years	3	3	3
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	62.7	63.5	61.1
standard deviation	± 9.25	± 3.51	± 11.36
Sex: Female, Male Units: Subjects			
Female	2	2	1
Male	10	4	8

Reporting group values	CXL-1427 7µg/kg/min	CXL-1427 12µg/kg/min	Total
Number of subjects	12	7	46

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)	8	6	32
From 65-84 years	4	1	14
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	61.6	48.3	
standard deviation	± 10.26	± 17.49	-
Sex: Female, Male Units: Subjects			
Female	0	2	7
Male	12	5	39

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received matching placebo intravenous (IV) infusion.	
Reporting group title	CXL-1427 3µg/kg/min
Reporting group description: Subjects received CXL-1427 3 microgram per kilogram per minute (µg/kg/min) IV infusion as 90 milliliter (mL) of dosing solution at a rate of 15 milliliter per hour (mL/hour) for six hours.	
Reporting group title	CXL-1427 5µg/kg/min
Reporting group description: Subjects received CXL-1427 5 µg/kg/min IV infusion as 90 mL of dosing solution at a rate of 15 mL/hour for six hours.	
Reporting group title	CXL-1427 7µg/kg/min
Reporting group description: Subjects received CXL-1427 7 µg/kg/min IV infusion as 150 mL of dosing solution at a rate of 25 mL/hour for six hours.	
Reporting group title	CXL-1427 12µg/kg/min
Reporting group description: Subjects received CXL-1427 12 µg/kg/min IV infusion as 180 mL of dosing solution at a rate of 30 mL/hour for six hours.	

Primary: Number of Participants with Treatment-Emergent Adverse Events

End point title	Number of Participants with Treatment-Emergent Adverse Events ^[1]
End point description: A treatment-emergent adverse event (TEAE) was defined as an AE with onset after the start of the study drug infusion at Hour 00:00 through 30 days after the stop of the study drug infusion. All TEAEs and pertinent subsets of TEAEs (e.g., TEAEs with onset during the infusion of study drug, serious TEAEs, etc.) were summarized by system organ class (SOC), preferred term (PT) and treatment group	
End point type	Primary
End point timeframe: 30 days following the initiation of treatment	
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 summary statistics were planned for this endpoint	

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: Participants				
At least one TEAE	3	5	5	7
At least one Severe TEAE	0	4	0	2
At least one Drug-related severe TEAE	0	0	0	0
At least one Serious TEAE	1	3	1	3
At least one Drug-related serious TEAE	0	0	0	0
At least one Fatal TEAE	0	1	0	0
At least one Drug-related fatal TEAE	0	0	0	0

At least one TEAE leading to drug interruption	0	0	0	0
At least one TEAE leading to drug discontinuation	0	0	0	0

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
At least one TEAE	3			
At least one Severe TEAE	1			
At least one Drug-related severe TEAE	0			
At least one Serious TEAE	1			
At least one Drug-related serious TEAE	0			
At least one Fatal TEAE	0			
At least one Drug-related fatal TEAE	0			
At least one TEAE leading to drug interruption	0			
At least one TEAE leading to drug discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Time Averaged Change from Baseline in Adjudicated Pulmonary Capillary Wedge Pressure (PCWP) During Infusion

End point title	Mean Time Averaged Change from Baseline in Adjudicated Pulmonary Capillary Wedge Pressure (PCWP) During Infusion
End point description:	
The effect of CXL-1427 on PCWP is presented as the mean time-averaged change from baseline over the course of infusion of CXL-1427 or placebo in adjudicated pulmonary capillary wedge pressure (PCWP) on a modified intent-to-treat population	
End point type	Primary
End point timeframe:	
Baseline, Hour 2, Hour 4, Hour 6, Hour 8 post infusion	

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-0.17 (± 2.35)	-3.00 (± 3.06)	-5.06 (± 3.93)	-4.42 (± 4.00)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-4.75 (± 3.50)			

Statistical analyses

Statistical analysis title	PCWP : CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0059
Method	Mixed models analysis

Statistical analysis title	PWCP: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Mixed models analysis

Statistical analysis title	PWCP: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0062
Method	Mixed models analysis

Statistical analysis title	PWCP: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0086
Method	Mixed models analysis

Primary: Mean Time-Averaged Change from Baseline in Adjudicated Pulmonary artery diastolic pressure (PAD) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Adjudicated Pulmonary artery diastolic pressure (PAD) During the Infusion
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End point description:

Pulmonary artery diastolic pressure (PAD) was measured by an indwelling PA catheter. Pulmonary artery diastolic pressure (PAD) approximates pulmonary capillary wedge pressure in normal individuals. The effects of CXL-1427 on time-averaged PAD during the course of the infusion are presented.

End point type	Primary
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End point timeframe:

Baseline, Hour 2, Hour 4, Hour 6, Hour 8 post infusion initiation

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-0.21 (± 3.35)	-3.69 (± 2.55)	-4.17 (± 4.02)	-2.67 (± 3.63)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-3.17 (± 1.82)			

Statistical analyses

Statistical analysis title	PAD: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0076
Method	Mixed models analysis

Statistical analysis title	PAD: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0052
Method	Mixed models analysis

Statistical analysis title	PAD: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1064
Method	Mixed models analysis

Statistical analysis title	PAD: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1151
Method	Mixed models analysis

Primary: Mean Time-Averaged Percent Change from Baseline in Cardiac Index (Fick)

End point title	Mean Time-Averaged Percent Change from Baseline in Cardiac Index (Fick)
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End point description:

Cardiac index is a measure of cardiac function, relating the cardiac output from the left ventricle in one minute to body surface area. It is calculated using the Fick principle, using oxygen consumption measured with a metabolic cart, hemoglobin levels, and the difference between arterial and superior vena cava oxygen saturation measured by co-oximetry. Cardiac index as calculated by the Fick method was performed using an assumed oxygen consumption value of 125 ml/min per m² of body surface area. i.e., an assumed Fick method.

End point type	Primary
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End point timeframe:

Baseline, Hour 2, Hour 4, Hour 6, Hour 8 post infusion initiation

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: Percentage				
arithmetic mean (standard deviation)	7.95 (± 16.15)	0.53 (± 18.12)	13.41 (± 23.53)	9.59 (± 11.91)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage				
arithmetic mean (standard deviation)	-9.58 (± 18.02)			

Statistical analyses

Statistical analysis title	CI (Fick): CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4241
Method	Mixed models analysis

Statistical analysis title	CI (Fick): CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4035
Method	Mixed models analysis

Statistical analysis title	CI (Fick): CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8308
Method	Mixed models analysis

Statistical analysis title	CI (Fick): CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.118
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Adjudicated Pulmonary Artery Systolic Pressure (PAS) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Adjudicated Pulmonary Artery Systolic Pressure (PAS) During the Infusion
End point description:	Pulmonary artery systolic pressure (PAS) was measured by an indwelling PA catheter. The effects of CXL-1427 on time-averaged PAS during the course of the infusion are presented
End point type	Secondary
End point timeframe:	Baseline, Hour 2, Hour 4, Hour 6, Hour 8 post infusion initiation

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-0.73 (± 3.73)	-6.42 (± 2.59)	-5.98 (± 5.31)	-6.26 (± 5.09)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-4.24 (± 5.24)			

Statistical analyses

Statistical analysis title	PAS: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0048
Method	Mixed models analysis

Statistical analysis title	PAS: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0022
Method	Mixed models analysis

Statistical analysis title	PAS: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0045
Method	Mixed models analysis

Statistical analysis title	PAS: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0294
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Adjudicated Right Atrial Pressure (RAP) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Adjudicated Right Atrial Pressure (RAP) During the Infusion
End point description:	The effects of CXL-1427 on time-averaged RAP during the course of the infusion are presented
End point type	Secondary
End point timeframe:	Baseline, Hour 2, Hour 4, Hour 6, Hour 8 post infusion initiation

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-0.03 (± 2.61)	-1.92 (± 2.91)	-2.08 (± 3.10)	-2.17 (± 2.42)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-4.60 (± 3.23)			

Statistical analyses

Statistical analysis title	RAP: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2022
Method	Mixed models analysis

Statistical analysis title	RAP: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0658
Method	Mixed models analysis

Statistical analysis title	RAP: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0741
Method	Mixed models analysis

Statistical analysis title	RAP: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0497
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Mean Arterial Blood Pressure (MAP) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Mean Arterial Blood Pressure (MAP) During the Infusion
End point description: Mean arterial pressure during infusion of CXL-1427 or placebo on a modified intent-to-treat population is presented	
End point type	Secondary
End point timeframe: Baseline, Hour 24 after infusion, Follow-up visit 1	

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-1.11 (± 5.01)	-5.84 (± 4.46)	-4.75 (± 10.93)	-7.16 (± 7.67)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-6.69 (± 5.67)			

Statistical analyses

Statistical analysis title	MAP: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1842
Method	Mixed models analysis

Statistical analysis title	MAP: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3328
Method	Mixed models analysis

Statistical analysis title	MAP: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1465
Method	Mixed models analysis

Statistical analysis title	MAP: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2799
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Systolic Blood Pressure (SBP) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Systolic Blood Pressure (SBP) During the Infusion
End point description: Mean Time-Averaged Change from Baseline in Systolic Blood Pressure during infusion of CXL-1427 or placebo on a modified intent-to-treat population is presented	
End point type	Secondary

End point timeframe:

Baseline, Hour 24 after infusion, Follow-up visit 1

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-3.15 (± 5.53)	-8.69 (± 4.43)	-2.41 (± 12.57)	-6.81 (± 9.54)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-4.64 (± 4.04)			

Statistical analyses

Statistical analysis title	SBP: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2499
Method	Mixed models analysis

Statistical analysis title	SBP: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8281
Method	Mixed models analysis

Statistical analysis title	SBP: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4121
Method	Mixed models analysis

Statistical analysis title	SBP: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8592
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Diastolic Blood Pressure (DBP) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Diastolic Blood Pressure (DBP) During the Infusion
End point description: Mean Time-Averaged Change from Baseline in Diastolic Blood Pressure during infusion of CXL-1427 or placebo on a modified intent-to-treat population is presented	
End point type	Secondary
End point timeframe: Baseline, Hour 24 after infusion, Follow-up visit 1	

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: mm Hg				
arithmetic mean (standard deviation)	-0.09 (± 8.30)	-4.42 (± 5.22)	-5.93 (± 11.07)	-7.33 (± 8.51)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm Hg				
arithmetic mean (standard deviation)	-7.71 (± 8.03)			

Statistical analyses

Statistical analysis title	DBP: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1391
Method	Mixed models analysis

Statistical analysis title	DBP : CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1724
Method	Mixed models analysis

Statistical analysis title	DBP: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1245
Method	Mixed models analysis

Statistical analysis title	DBP: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.169
Method	Mixed models analysis

Secondary: Mean Time-Averaged Change from Baseline in Heart Rate (HR) During the Infusion

End point title	Mean Time-Averaged Change from Baseline in Heart Rate (HR) During the Infusion
End point description: Mean Time-Averaged Change from Baseline in Heart Rate during infusion of CXL-1427 or placebo on a modified intent-to-treat population is presented	
End point type	Secondary

End point timeframe:

Baseline, Hour 24 after infusion, Follow-up visit 1

End point values	Placebo	CXL-1427 3µg/kg/min	CXL-1427 5µg/kg/min	CXL-1427 7µg/kg/min
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	9	12
Units: Beats/min				
arithmetic mean (standard deviation)	-0.79 (± 6.34)	1.06 (± 3.74)	-3.09 (± 6.84)	1.00 (± 7.08)

End point values	CXL-1427 12µg/kg/min			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Beats/min				
arithmetic mean (standard deviation)	-4.52 (± 16.92)			

Statistical analyses

Statistical analysis title	HR: CXL-1427 3ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 3µg/kg/min
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4936
Method	Mixed models analysis

Statistical analysis title	HR: CXL-1427 5ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 5µg/kg/min
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.992
Method	Mixed models analysis

Statistical analysis title	HR: CXL-1427 7ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 7µg/kg/min

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2789
Method	Mixed models analysis

Statistical analysis title	HR: CXL-1427 12ug/kg/min vs Placebo
Comparison groups	Placebo v CXL-1427 12µg/kg/min
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.91
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were reported from signed of informed consent form through 30 days post final infusion of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received matching placebo intravenous (IV) infusion.

Reporting group title	CXL-1427 3 µg/kg/min
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Reporting group description:

Subjects received CXL-1427 3 microgram per kilogram per minute (µg/kg/min) IV infusion as 90 milliliter (mL) of dosing solution at a rate of 15 milliliter per hour (mL/hour) for six hours.

Reporting group title	CXL-1427 5 µg/kg/min
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Reporting group description:

Subjects received CXL-1427 5 µg/kg/min IV infusion as 90 mL of dosing solution at a rate of 15 mL/hour for six hours.

Reporting group title	CXL-1427 7 µg/kg/min
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Reporting group description:

Subjects received CXL-1427 7 µg/kg/min IV infusion as 150 mL of dosing solution at a rate of 25 mL/hour for six hours.

Reporting group title	CXL-1427 12 µg/kg/min
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Reporting group description:

Subjects received CXL-1427 12 µg/kg/min IV infusion as 180 mL of dosing solution at a rate of 30 mL/hour for six hours.

Serious adverse events	Placebo	CXL-1427 3 µg/kg/min	CXL-1427 5 µg/kg/min
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	3 / 6 (50.00%)	1 / 9 (11.11%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Cardiac disorders			
Atrial flutter			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders Respiratory failure alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Skin and subcutaneous tissue disorders Toxic epidermal necrolysis alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders Renal failure alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations Rhinovirus infection alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CXL-1427 7 µg/kg/min	CXL-1427 12 µg/kg/min	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	1 / 7 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial flutter			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Rhinovirus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	CXL-1427 3 µg/kg/min	CXL-1427 5 µg/kg/min
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	6 / 6 (100.00%)	6 / 9 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of thyroid gland			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	3 / 9 (33.33%)
occurrences (all)	1	0	3
General disorders and administration site conditions			
Catheter site haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			

Psychotic disorder alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 6 (16.67%) 1	0 / 9 (0.00%) 0
Investigations Blood creatinine increased alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 6 (0.00%) 0	0 / 9 (0.00%) 0
Injury, poisoning and procedural complications Vascular pseudoaneurysm alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 6 (0.00%) 0	0 / 9 (0.00%) 0
Cardiac disorders Atrial flutter alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Atrioventricular block complete alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Cardiac failure alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Cardiac failure congestive alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Cardiorenal syndrome alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1

<p>Low cardiac output syndrome</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>	<p>0 / 6 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p>
<p>Tachycardia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>	<p>1 / 6 (16.67%)</p> <p>1</p>	<p>0 / 9 (0.00%)</p> <p>0</p>
<p>Ventricular tachycardia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>	<p>0 / 6 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p>
<p>Nervous system disorders</p> <p>Dizziness</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Syncope</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p> <p>0 / 12 (0.00%)</p> <p>0</p> <p>0 / 12 (0.00%)</p> <p>0</p>	<p>0 / 6 (0.00%)</p> <p>0</p> <p>0 / 6 (0.00%)</p> <p>0</p> <p>0 / 6 (0.00%)</p> <p>0</p>	<p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>
<p>Skin and subcutaneous tissue disorders</p> <p>Ecchymosis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toxic epidermal necrolysis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p> <p>0 / 12 (0.00%)</p> <p>0</p>	<p>0 / 6 (0.00%)</p> <p>0</p> <p>1 / 6 (16.67%)</p> <p>1</p>	<p>0 / 9 (0.00%)</p> <p>0</p> <p>0 / 9 (0.00%)</p> <p>0</p>
Renal and urinary disorders			

Renal failure alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 6 (0.00%) 0	0 / 9 (0.00%) 0
Infections and infestations Rhinovirus infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Urinary tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	1 / 6 (16.67%) 1 1 / 6 (16.67%) 1	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0
Metabolism and nutrition disorders Dehydration alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Hypoglycaemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0

Non-serious adverse events	CXL-1427 7 µg/kg/min	CXL-1427 12 µg/kg/min	
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 12 (58.33%)	4 / 7 (57.14%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Benign neoplasm of thyroid gland alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Vascular disorders Hypotension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	

General disorders and administration site conditions Catheter site haemorrhage alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Chest pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Pleural effusion alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Respiratory failure alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	
Psychiatric disorders Psychotic disorder alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 7 (0.00%) 0	
Investigations Blood creatinine increased alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 7 (0.00%) 0	
Injury, poisoning and procedural complications Vascular pseudoaneurysm alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 0 / 7 (0.00%) 0	
Cardiac disorders			

Atrial flutter			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block complete			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cardiac failure congestive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Cardiorenal syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Low cardiac output syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Ventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	1 / 7 (14.29%) 1	
Syncope alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 7 (14.29%) 1	
Skin and subcutaneous tissue disorders Ecchymosis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Toxic epidermal necrolysis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 7 (0.00%) 0	
Renal and urinary disorders Renal failure alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 7 (0.00%) 0	
Infections and infestations Rhinovirus infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 7 (0.00%) 0	
Urinary tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 7 (0.00%) 0	
Metabolism and nutrition disorders			

Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported