Clinical trial results:
Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, pharmacodynamics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction

Summary

EudraCT number	2015-004207-22
Trial protocol	DE FI NL SE NO ES GB CZ IT FR BG PL HU HR AT PT RO
Global end of trial date	03 January 2022

Results information

Result version number	v1 (current)
This version publication date	17 July 2022
First version publication date	17 July 2022

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2319

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02678312
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, 41 613241111, novartis.email@novartis.com
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000316-PIP03-20
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study consists of two parts (Part 1 and Part 2). The objective of Part 1 was to evaluate the way the body absorbs, distributes and removes the drug LCZ696. This would help determine the proper dose of LCZ696 for Part 2 of the study. The objective for Part 2 was to compare the effectiveness and safety of LCZ696 with enalapril in pediatric heart failure participants over 52 weeks of treatment.

Protection of trial subjects:

Parents or guardians of all participants in this pediatric study were required to read and sign the Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 27
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 16
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Jordan: 1
Country: Number of subjects enrolled	Korea, Republic of: 19

Country: Number of subjects enrolled	Lebanon: 10
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	United States: 137
Worldwide total number of subjects	393
EEA total number of subjects	98

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)	80
Children (2-11 years)	180
Adolescents (12-17 years)	133
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

393 participants were enrolled. Part 1:26 unique participants[Dose cohort 1:LCZ696 0.8 milligrams per kilogram(mg/kg)(Groups 1 and 2:age 6 to <18 years(yrs),and 1 to < 6yrs, respectively)or 0.4 mg/kg(Group 3:1 month to < 1yr), Dose cohort 2:LCZ696 3.1 mg/kg(Groups 1 and 2) or 1.6 mg/kg(Group 3)].Part 2:377 were enrolled. 10 participants from Part 1

Pre-assignment

Screening details:

Out of 26, 17 participants received drug in Dose cohort 1(Period 1). Out of 17 participants from Dose cohort 1, 9 entered Dose cohort 2(Period 2). About 9 participants directly entered Dose cohort 2. There were 2 participants from Dose cohort 2 received 3.1 mg/kg on Day 1 (Period 2) followed by 0.8 mg/kg, who entered Dose cohort S.

Period 1

Period 1 title	Part 1 Open label Epoch- Period 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Part 1: Dose Cohort 1

Arm description:

Participants received LCZ696 0.4 mg/kg (age group 3 {1 month to < 1 year}) or 0.8 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}), based on age, given as a single oral dose on Day 1 of period 1.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	sacubitiril/valsartan
Pharmaceutical forms	Granules for oral solution
Routes of administration	Oral use

Dosage and administration details:

Granules for oral solution

Number of subjects in period 1	Part 1: Dose Cohort 1
Started	17
Completed	14
Not completed	3
Physician decision	1
Adverse event, non-fatal	1
Lost to follow-up	1

Period 2

Period 2 title	Part 1 Open label Epoch- Period 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Part 1: Dose Cohort 2

Arm description:

Participants received LCZ696 1.6 mg/kg (age group 3 {1 month to < 1 year}) or 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}), based on age, given as a single oral dose on Day 1 of period 2.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	sacubitiril/valsartan
Pharmaceutical forms	Granules for oral solution
Routes of administration	Oral use

Dosage and administration details:

Granules for oral solution

Arm title	Part 1: Dose Cohort S

Arm description:

Participants in the dose cohort 2 who received LCZ696 3.1 mg/kg on Day 1 of period 2 and later received LCZ696 0.8 mg/kg, within period 2.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	sacubitiril/valsartan
Pharmaceutical forms	Granules for oral solution
Routes of administration	Oral use

Dosage and administration details:

Granules for oral solution

Number of subjects in period 2	Part 1: Dose Cohort 2	Part 1: Dose Cohort S
Started	18	2
Completed	18	2

Period 3

Period 3 title	Part 2 Double Blind Epoch
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	No
Arm title	Part 2: LCZ696

Arm description:

Participants randomised to receive LCZ696 received LCZ696 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}) or 2.3 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, twice a day (BID) for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	sacubitiril/valsartan
Pharmaceutical forms	Granules, Tablet, Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

LCZ696 tablets, granules, or liquid formulation from tablets

Arm title	Part 2: Enalapril

Arm description:

Participants randomised to receive enalapril received enalapril 0.2 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}) or 0.15 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, BID, for 52 weeks.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules, Tablet, Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

LCZ696 tablets, granules, or liquid formulation from tablets

Number of subjects in period 3	Part 2: LCZ696	Part 2: Enalapril
Started	187	188
Completed	169	164
Not completed	18	24
Adverse event, serious fatal	8	12
Adverse event, non-fatal	1	2
Technical Problems	4	2
Subject/guardian Decision	5	6
Lost to follow-up	-	2

Baseline characteristics

Reporting groups[1]

Reporting group title	Part 1: Dose Cohort 1

Reporting group description:

Participants received LCZ696 0.4 mg/kg (age group 3 {1 month to < 1 year}) or 0.8 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}), based on age, given as a single oral dose on Day 1 of period 1.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two participants in Part 2 who were enrolled but did not receive the study drug are not included.

Reporting group values	Part 1: Dose Cohort 1	Total	
Number of subjects	17	17	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	5.65		
standard deviation	± 5.283	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	9	9	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	2	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	9	9	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	9	9	
Unknown or Not Reported	6	6	

Subject analysis sets

Subject analysis set title	Part 1: Dose Cohort 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 1.6 mg/kg (age group 3 {1 month to < 1 year}) or 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}, based on age, given as a single oral dose on Day 1 of period 2.

Subject analysis set title	Part 1: Dose Cohort S

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the dose cohort 2 who received LCZ696 3.1 mg/kg on Day 1 of period 2 and later received LCZ696 0.8 mg/kg, within period 2.

Subject analysis set title	Part 2: LCZ696
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomised to LCZ696 received LCZ696 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years} or 2.3 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, twice a day (BID) for 52 weeks.

Subject analysis set title	Part 2: Enalapril
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomised to enalapril received enalapril 0.15 mg/kg or 0.2 mg/kg based on age, orally, BID, and PTM LCZ696 bid for 52 weeks.

Subject analysis set title	LCZ696: 0.8 mg/kg (Age Group 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.8 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from the age of 6 to less than 18 years were included in this group.

Subject analysis set title	LCZ696: 0.8 mg/kg (Age Group 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.8 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from age of 1 to less than 6 years were included in this group.

Subject analysis set title	LCZ696: 3.1 mg/kg (Age Group 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 3.1 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from the age of 6 to less than 18 years were included in this group.

Subject analysis set title	LCZ696: 3.1 mg/kg (Age Group 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 3.1 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from age of 1 to less than 6 years were included in this group.

Subject analysis set title	LCZ696: 0.4 mg/kg (Age Group 3)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.4 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from the age of 1 month to less than 1 year were included in this group.

Subject analysis set title	LCZ696: 1.6 mg/kg (Age Group 3)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 1.6 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from age 1 month to 1 year were included in this group.

Subject analysis set title	LCZ696 (Part 1 and 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.4 mg/kg (age group 3) or 0.8 mg/kg (age group 1 and 2) on Day 1 of Period 1 and 1.6 mg/kg (age group 3) or 3.1 mg/kg (age group 1 and 2) on Day 1 of Period 2, based on age, given as a single oral dose in Part 1. Followed by Part 1, participants were enrolled in Part 2 and received LCZ696 2.3 mg/kg (age group 3) or 3.1 mg/kg (age group 1 and 2), based on age, orally, twice a day (BID) for 52 weeks in Part 2.

Reporting group values	Part 1: Dose Cohort 2	Part 1: Dose Cohort S	Part 2: LCZ696
Number of subjects	18	2	187
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	5.60	1.55	8.00
standard deviation	± 5.849	± 0.636	± 5.471
Gender categorical			
Units: Subjects			
Female	6	0	98
Male	12	2	89
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	0	3
Asian	4	0	57
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	1	23
White	7	0	87
More than one race	0	0	0
Unknown or Not Reported	2	1	17
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	0	24
Not Hispanic or Latino	10	1	134
Unknown or Not Reported	7	1	28

Reporting group values	Part 2: Enalapril	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)
Number of subjects	188	7	8
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	8.26	0	0
standard deviation	± 5.718	± 0	± 0
Gender categorical			
Units: Subjects			
Female	95	0	0
Male	93	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2	0	0
Asian	45	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	25	0	0
White	93	0	0
More than one race	0	0	0

Unknown or Not Reported	23	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	0	0
Not Hispanic or Latino	125	0	0
Unknown or Not Reported	48	0	0

Reporting group values	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)	LCZ696: 0.4 mg/kg (Age Group 3)
Number of subjects	7	6	4
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender categorical Units: Subjects			
Female	0	0	0
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	LCZ696: 1.6 mg/kg (Age Group 3)	LCZ696 (Part 1 and 2)	
Number of subjects	5	203	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Gender categorical Units: Subjects			
Female	0	0	
Male	0	0	

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Part 1: Dose Cohort 1
Reporting group description:	
Participants received LCZ696 0.4 mg/kg (age group 3 {1 month to < 1 year}) or 0.8 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}), based on age, given as a single oral dose on Day 1 of period 1.	
Reporting group title	Part 1: Dose Cohort 2
Reporting group description:	
Participants received LCZ696 1.6 mg/kg (age group 3 {1 month to < 1 year}) or 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}), based on age, given as a single oral dose on Day 1 of period 2.	
Reporting group title	Part 1: Dose Cohort S
Reporting group description:	
Participants in the dose cohort 2 who received LCZ696 3.1 mg/kg on Day 1 of period 2 and later received LCZ696 0.8 mg/kg, within period 2.	
Reporting group title	Part 2: LCZ696
Reporting group description:	
Participants randomised to receive LCZ696 received LCZ696 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}) or 2.3 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, twice a day (BID) for 52 weeks.	
Reporting group title	Part 2: Enalapril
Reporting group description:	
Participants randomised to receive enalapril received enalapril 0.2 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}) or 0.15 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, BID, for 52 weeks.	
Subject analysis set title	Part 1: Dose Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received LCZ696 1.6 mg/kg (age group 3 {1 month to < 1 year}) or 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}, based on age, given as a single oral dose on Day 1 of period 2.	
Subject analysis set title	Part 1: Dose Cohort S
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants in the dose cohort 2 who received LCZ696 3.1 mg/kg on Day 1 of period 2 and later received LCZ696 0.8 mg/kg, within period 2.	
Subject analysis set title	Part 2: LCZ696
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants randomised to LCZ696 received LCZ696 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years} or 2.3 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, twice a day (BID) for 52 weeks.	
Subject analysis set title	Part 2: Enalapril
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants randomised to enalapril received enalapril 0.15 mg/kg or 0.2 mg/kg based on age, orally, BID, and PTM LCZ696 bid for 52 weeks.	
Subject analysis set title	LCZ696: 0.8 mg/kg (Age Group 1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received LCZ696 0.8 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from the age of 6 to less than 18 years were included in this group.	
Subject analysis set title	LCZ696: 0.8 mg/kg (Age Group 2)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.8 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from age of 1 to less than 6 years were included in this group.

Subject analysis set title	LCZ696: 3.1 mg/kg (Age Group 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 3.1 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from the age of 6 to less than 18 years were included in this group.

Subject analysis set title	LCZ696: 3.1 mg/kg (Age Group 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 3.1 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from age of 1 to less than 6 years were included in this group.

Subject analysis set title	LCZ696: 0.4 mg/kg (Age Group 3)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.4 mg/kg, given as a single oral dose on Day 1 of Period 1 in Part 1. Participants ranging from the age of 1 month to less than 1 year were included in this group.

Subject analysis set title	LCZ696: 1.6 mg/kg (Age Group 3)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 1.6 mg/kg, given as a single oral dose on Day 1 of Period 2 in Part 1. Participants ranging from age 1 month to 1 year were included in this group.

Subject analysis set title	LCZ696 (Part 1 and 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received LCZ696 0.4 mg/kg (age group 3) or 0.8 mg/kg (age group 1 and 2) on Day 1 of Period 1 and 1.6 mg/kg (age group 3) or 3.1 mg/kg (age group 1 and 2) on Day 1 of Period 2, based on age, given as a single oral dose in Part 1. Followed by Part 1, participants were enrolled in Part 2 and received LCZ696 2.3 mg/kg (age group 3) or 3.1 mg/kg (age group 1 and 2), based on age, orally, twice a day (BID) for 52 weeks in Part 2.

Primary: Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Maximum Drug Concentration in Plasma (Cmax)

End point title	Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Maximum Drug Concentration in Plasma (Cmax)[1]

End point description:

As prespecified in protocol and statistical analysis plan (SAP) the analysis of this outcome measure was done based on dose of LCZ696 administered within the different age groups. Part 1 Pharmacokinetic (PK) Set included all Part 1 eligible set (ELG1) participants with at least one dose of study drug during Part 1 of the study, at least one available valid (i.e., not flagged for exclusion) PK concentration measurement during Part 1 of the study, and with no protocol deviations with relevant impact on PK data during Part 1 of the study.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	6
Units: nanograms per milliliter (ng/ml)				
arithmetic mean (standard deviation)				
Sacubitril	523 (± 390)	179 (± 97)	1970 (± 1666)	549 (± 298)
LBQ657	1951 (± 839)	1359 (± 711)	6707 (± 1887)	5453 (± 1032)
Valsartan	1271 (± 1011)	1112 (± 583)	4035 (± 1678)	4935 (± 1268)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: nanograms per milliliter (ng/ml)				
arithmetic mean (standard deviation)				
Sacubitril	124 (± 80)	433 (± 181)		
LBQ657	632 (± 89)	2326 (± 629)		
Valsartan	440 (± 275)	2487 (± 1564)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Time to Maximum Plasma Concentration (Tmax)

End point title	Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Time to Maximum Plasma Concentration (Tmax)[2]

End point description:

As prespecified in protocol and SAP the analysis of this outcome measure was done based on dose of LCZ696 administered within the different age groups. Participants in the Part 1 PK Set were analyzed.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	6
Units: Hours				
arithmetic mean (standard deviation)				

Sacubitril	1.1 (± 1.3)	1.2 (± 0.5)	0.8 (± 0.3)	1.2 (± 0.4)
LBQ657	4.0 (± 2.0)	2.9 (± 1.1)	2.9 (± 1.1)	3.6 (± 3.2)
Valsartan	1.7 (± 1.1)	2.1 (± 1.4)	2.6 (± 1.0)	1.9 (± 0.4)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: Hours				
arithmetic mean (standard deviation)				
Sacubitril	1.1 (± 0.1)	1.0 (± 0.0)		
LBQ657	2.8 (± 1.6)	3.6 (± 0.9)		
Valsartan	1.8 (± 1.5)	1.8 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacokinetics of LCZ696 analytes (sacubitril, LBQ657, and valsartan): Area Under the Plasma Concentration-time Curve from Time Zero to Infinity (AUCinf)

End point title	Part 1: Pharmacokinetics of LCZ696 analytes (sacubitril, LBQ657, and valsartan): Area Under the Plasma Concentration-time Curve from Time Zero to Infinity (AUCinf)[3]

End point description:

As prespecified in protocol and SAP the analysis of this outcome measure was done based on dose of LCZ696 administered within the different age groups. Participants in the Part 1 PK Set were analyzed.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	6
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Sacubitril	690 (± 410)	494 (± 286)	3021 (± 1814)	1214 (± 684)
LBQ657	48264 (± 22939)	31042 (± 17259)	150440 (± 49515)	127625 (± 35634)
Valsartan	13540 (± 12962)	11036 (± 7031)	40733 (± 21003)	48561 (± 21163)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Sacubitril	270 (± 182)	1063 (± 266)		
LBQ657	15835 (± 2912)	62377 (± 16035)		
Valsartan	3923 (± 1424)	26170 (± 16826)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacokinetics of LCZ696 analytes (sacubitril, LBQ657, and valsartan): Number of Participants With Area Under the Plasma Concentration-time Curve from Time Zero to Last (AUClast)

End point title	Part 1: Pharmacokinetics of LCZ696 analytes (sacubitril, LBQ657, and valsartan): Number of Participants With Area Under the Plasma Concentration-time Curve from Time Zero to Last (AUClast)[4]

End point description:

Participants in the Part 1 PK Set were analyzed.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	6
Units: participants	7	8	7	6

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		

Units: participants	4	5		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Clearance from Plasma (CL/F)

End point title	Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril, LBQ657, and valsartan): Clearance from Plasma (CL/F)[5]

End point description:

As prespecified in protocol and SAP the analysis of this outcome measure was done based on dose of LCZ696 administered within the different age groups. CL/F was not estimated for LBQ657 as it is a metabolite. Participants in the Part 1 PK Set were analyzed.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	6
Units: L/hr/kg				
arithmetic mean (standard deviation)				
Sacubitril	0.73 (± 0.35)	1.19 (± 0.96)	0.63 (± 0.28)	1.67 (± 1.01)
Valsartan	0.06 (± 0.05)	0.07 (± 0.09)	0.06 (± 0.06)	0.04 (± 0.01)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: L/hr/kg				
arithmetic mean (standard deviation)				
Sacubitril	1.19 (± 1.11)	1.67 (± 1.01)		
Valsartan	0.06 (± 0.02)	0.05 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril): Time Required to Drug Concentration to Decrease by Half (T 1/2)

End point title	Part 1: Pharmacokinetics of LCZ696 Analytes (sacubitril): Time Required to Drug Concentration to Decrease by Half (T 1/2)[6]

End point description:

As prespecified in protocol and SAP the analysis of this outcome measure was done based on dose of LCZ696 administered within the different age groups. T1/2 for other analytes of LCZ696 (LBQ657 and Valsartan) was not estimable due to short sample collection timeframe. Part 1 PK Set. The overall number of participants analyzed is the number of participants with data available for this endpoint.

End point type	Primary

End point timeframe:

Age group 1: Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age group 2 and 3: Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	6	4
Units: Hours				
median (full range (min-max))	1.26 (0.95 to 2.36)	1.53 (1.40 to 1.65)	1.34 (1.16 to 1.60)	1.51 (1.34 to 1.70)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	3		
Units: Hours				
median (full range (min-max))	(to)	1.33 (1.16 to 1.64)		

Notes:

[7] - Data is not available as 0 participants were analysed.

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma B-type Natriuretic Peptide (BNP)

End point title	Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma B-type Natriuretic Peptide (BNP)[8]

End point description:

Biomarkers were used to assess the PD effects of LCZ696. Blood biomarkers of interest included plasma BNP. Biomarkers related to heart failure or the mechanism of action of the study drug were measured. Summary statistics for change from baseline at each time point is presented. The baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) prior to (the first dose time of

the study drug within the dose associated period). For each post-dose time point, participants are included if and only if the participant has both pre-dose assessment and current time point assessment observed. Part 1 PD set (PD1) included all participants who completed the Part 1 screening phase and had at least one dose of study drug during Part 1 of the study, at least one available PD measurement during Part 1 of the study, with no protocol deviations with relevant impact.9999= The 95% confidence interval (CI) was not estimable for one participant. CFB= Change From Baseline.

End point type	Primary

End point timeframe:

Baseline (0 hrs pre dose), 4 and 8 hrs post dose on Day 1 of Period 1 and Period 2

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	7	3
Units: pmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=6,6,7,3,3,4)	100.87 (49.84 to 204.13)	63.80 (8.65 to 470.81)	97.52 (51.59 to 184.32)	120.51 (5.21 to 2787.44)
CFB:4 hrs post dose (n=6,4,7,1,3,4)	1.31 (0.93 to 1.85)	1.60 (0.21 to 11.95)	1.22 (0.94 to 1.58)	0.62 (-9999 to 9999)
CFB:8 hrs post dose (n=5,4,1,1,3,2)	1.32 (0.92 to 1.88)	1.21 (0.21 to 7.04)	0.97 (0.70 to 1.34)	0.80 (-9999 to 9999)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: pmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=6,6,7,3,3,4)	21.20 (2.14 to 210.41)	129.29 (9.45 to 1768.43)		
CFB:4 hrs post dose (n=6,4,7,1,3,4)	0.77 (0.56 to 1.05)	1.09 (0.61 to 1.93)		
CFB:8 hrs post dose (n=5,4,1,1,3,2)	0.59 (0.27 to 1.30)	0.55 (0.15 to 2.02)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma N-terminal pro-brain Natriuretic Peptide (NTproBNP)

End point title	Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma N-

	terminal pro-brain Natriuretic Peptide (NTproBNP)[9]

End point description:

Biomarkers were used to assess the PD effects of LCZ696. Blood biomarkers of potential interest included plasma NTproBNP. Biomarkers related to heart failure or the mechanism of action of the study drug were measured. Summary statistics for change from baseline at each time point is presented. The baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) prior to (the first dose time of the study drug within the dose associated period). For each post-dose time point, participants are included if and only if the participant has both pre-dose assessment and current time point assessment observed. Part 1 PD set. The overall number of participants analyzed is the number of participants with data available for this endpoint.

End point type	Primary

End point timeframe:

Baseline (0 hrs pre dose) and optional 24 hours post dosing on Day 1 of Period 1 and Period 2

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	0[10]	7	0[11]
Units: pg/mL				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,0,7,0,4,5)	2385.34 (1186.13 to 4796.98)	(to)	2179.94 (932.77 to 5094.69)	(to)
CFB:24 hrs post dose (n=3,0,0,0,2,2)	0.74 (0.31 to 1.78)	(to)	0 (0 to 0)	(to)

Notes:

[10] - Data is not available as 0 participants were analysed.

[11] - Data is not available as 0 participants were analysed.

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	5		
Units: pg/mL				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,0,7,0,4,5)	961.76 (125.65 to 7361.70)	5086.37 (683.53 to 37849.4)		
CFB:24 hrs post dose (n=3,0,0,0,2,2)	0.59 (0.00 to 134.25)	0.41 (0.34 to 0.48)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma Cyclic Guanosine Monophosphate (cGMP)

End point title	Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Plasma Cyclic Guanosine Monophosphate (cGMP)[12]

End point description:

Biomarkers were used to assess the PD effects of LCZ696. Blood biomarkers of potential interest included plasma cGMP. Biomarkers related to heart failure or the mechanism of action of the study drug were measured. Summary statistics for change from baseline at each time point is presented. The baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) prior to (the first dose time of the study drug within the dose associated period). For each post-dose time point, participants are included if and only if the participant has both pre-dose assessment and current time point assessment observed. Part 1 PD set. The overall number of participants analyzed is the number of participants with data available for this endpoint.

End point type	Primary

End point timeframe:

Baseline (0 hrs pre dose), 4 and 8 hrs post dose on Day 1 of Period 1 and Period 2

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	6	7	4
Units: nmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,6,7,4,2,3)	18.18 (12.01 to 27.51)	21.41 (12.83 to 35.71)	12.20 (8.13 to 18.32)	24.55 (18.37 to 32.82)
CFB:4 hrs post dose (n=7,6,7,4,2,3)	1.30 (0.89 to 1.90)	0.90 (0.50 to 1.62)	1.54 (1.12 to 2.10)	1.02 (0.52 to 2.01)
CFB:8 hrs post dose (n=7,4,7,4,2,3)	1.17 (0.91 to 1.50)	0.92 (0.66 to 1.29)	1.60 (1.10 to 2.31)	0.40 (0.02 to 8.86)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	3		
Units: nmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,6,7,4,2,3)	13.38 (0.05 to 3883.59)	22.84 (12.51 to 41.68)		
CFB:4 hrs post dose (n=7,6,7,4,2,3)	0.80 (0.00 to 618.02)	0.78 (0.27 to 2.22)		
CFB:8 hrs post dose (n=7,4,7,4,2,3)	0.79 (0.00 to 230.10)	0.79 (0.29 to 2.18)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Urine cGMP

End point title	Part 1: Pharmacodynamics of LCZ696 Analytes (Sacubitril, LBQ657, and Valsartan): Change From Baseline in Urine cGMP[13]

End point description:

Biomarkers were used to assess the PD effects of LCZ696. Blood biomarkers of potential interest included urine cGMP. Biomarkers related to heart failure or the mechanism of action of the study drug were measured. Summary statistics for change from baseline at each time point is presented. The baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) prior to (the first dose time of the study drug within the dose associated period). For each post-dose time point, participants are included if and only if the participant has both pre-dose assessment and current time point assessment observed. Part 1 PD set. The overall number of participants analyzed is the number of participants with data available for this endpoint. 9999= The 95% CI was not estimable for one participant

End point type	Primary

End point timeframe:

Baseline (0 hrs pre dose), 4 and 8 hrs post dose on Day 1 of Period 1 and Period 2

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	LCZ696: 0.8 mg/kg (Age Group 1)	LCZ696: 0.8 mg/kg (Age Group 2)	LCZ696: 3.1 mg/kg (Age Group 1)	LCZ696: 3.1 mg/kg (Age Group 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	3	6	3
Units: nmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,3,6,3,1,5)	1055.56 (352.98 to 3156.55)	1349.91 (118.48 to 15380.33)	914.57 (311.65 to 2683.88)	1123.69 (75.21 to 16789.03)
CFB:4 to 8 hrs hrs post dose (n=7,3,6,3,2,4)	1.42 (0.38 to 5.32)	0.80 (0.02 to 27.03)	1.79 (0.65 to 4.96)	2.17 (0.10 to 45.16)

End point values	LCZ696: 0.4 mg/kg (Age Group 3)	LCZ696: 1.6 mg/kg (Age Group 3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	5		
Units: nmol/L				
geometric mean (confidence interval 95%)				
Baseline:0 hrs pre dose (n=7,3,6,3,1,5)	485.00 (-9999 to 9999)	386.32 (134.04 to 1113.42)		
CFB:4 to 8 hrs hrs post dose (n=7,3,6,3,2,4)	0.92 (0.02 to 51.75)	1.98 (0.51 to 7.63)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Percentage of Participants With Worst Event in Each Category Based on Global Ranking

End point title	Part 2: Percentage of Participants With Worst Event in Each Category Based on Global Ranking[14]

End point description:

Global ranking=5 categories ranking worst to best outcome: Category 1:Death; United Network for Organ Sharing(UNOS) status 1A listing for heart transplant or equivalent;ventricular assist device (VAD)/extracorporeal membrane oxygenation(ECMO)/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study.Category 2:Worsening HF(WHF)=by signs and symptoms of WHF that requires an intensification of HF therapy.Category 3:Worsened;worse New York Heart Association(NYHA)/Ross or worse Patient Global Impression of Severity(PGIS) further ranking by Pediatric Quality of Life Inventory(PedsQL) physical functioning domain.Category 4:Unchanged; unchanged NYHA/Ross and unchanged PGIS further ranking by PedsQL physical functioning domain.Category 5: Improved; improved NYHA/Ross or improved PGIS (neither can be worse) further ranking by PedsQL physical functioning domain.Participants with worst event in each category are reported here.Participants in full analysis set.

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for the primary end point.

End point values	Part 2: LCZ696	Part 2: Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: percentage of participants				
number (not applicable)				
Category 1	10.16	15.96		
Category 2	9.63	4.79		
Category 3	6.95	5.85		
Category 4	20.86	26.60		
Category 5	39.57	35.64		
Missing	12.83	11.17		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Part 1: Percentage of Participants with Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related, that occurs after a participant provides informed consent. TEAEs during part 1 are defined as any recorded AE with its start date (recorded or imputed) later than or equal to the date of the first dose of the study drug within part 1 and its start date prior to or equal to the end date of the part 1. Part 1 Safety Analysis Set (SAF1) included all participants who completed the Part 1 screening phase and received at least one dose of study drug during Part 1 of the study.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study drug in Part 1

End point values	Part 1: Dose Cohort 1	Part 1: Dose Cohort 2	Part 1: Dose Cohort S	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	18	2	
Units: percentage of participants				
number (not applicable)	41.18	55.56	50.00	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Exposure-adjusted Incidence Rate of Category 1 or Category 2 Event

End point title	Part 2: Exposure-adjusted Incidence Rate of Category 1 or Category 2 Event

End point description:

The exposure adjusted incidence rate is calculated as number of participants with at least one event divided by total participant years across all participants. Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study. Category 2: WHF; defined by signs and symptoms of WHF that requires an intensification of HF therapy. Participants in the full analysis set were analyzed. Number analyzed are participants with at least one event in each category.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Part 2: LCZ696	Part 2: Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	33		
Units: participant per participant years				
number (confidence interval 95%)				
Category 1 or 2	20.133 (13.9430 to 28.1344)	20.042 (13.7960 to 28.1464)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 2: LCZ696 v Part 2: Enalapril

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7958 [15]
Method	Cox Proportional Hazard
Parameter estimate	Cox proportional hazard
Point estimate	1.0655
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6589
upper limit	1.7232

Notes:

[15] - The adjusted hazard ratio and the p-values are based on Cox proportional hazard model, stratified by modified age group with treatment and NYHA/ROSS class group included as factor.

Secondary: Part 2: Percentage of Participants With Change from Baseline in New York Heart Association (NYHA)/Ross Functional Class

End point title	Part 2: Percentage of Participants With Change from Baseline in New York Heart Association (NYHA)/Ross Functional Class

End point description:

NYHA classification=subjective physician's assessment of participant's functional capacity and symptomatic status and can change frequently over time.NYHA=tool that classifies participants with heart failure into one of four classes according to their degree of symptoms at rest and with activity.Class I:No limitations of physical activity.Class 2:May experience fatigue,palpitations,dyspnea,or angina during moderate exercise but not during rest.Class 3:Symptoms with minimal exertion that interfere with normal daily activity.Class 4:Unable to carry out any physical activity because they typically have symptoms of HF at rest that worsen with any exertion.Participants with change from baseline were classified as improved (shifted from higher to lower class),unchanged (no change in class) or worsened (shifted from lower to higher class).Participants in the full analysis set with available data were analyzed.n=number of participants with data available for analyses at specific timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 24, 36, and 52

End point values	Part 2: LCZ696	Part 2: Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: percentage of participants				
number (not applicable)				
CFB at Week 4: Improved (n=183,184)	14.21	15.67		
CFB at Week 4: Unchanged (n=183,184)	84.15	82.61		
CFB at Week 4: Worsened (n=183,184)	1.64	1.63		
CFB at Week 12: Improved (n=180,180)	23.89	25.56		
CFB at Week 12: Unchanged (n=180,180)	70.56	67.78		
CFB at Week 12: Worsened (n=180,180)	5.56	6.67		
CFB at Week 24: Improved (n=178,172)	26.97	27.91		

CFB at Week 24: Unchanged (n=178,172)	64.04	63.95		
CFB at Week 24: Worsened (n=178,172)	8.99	8.14		
CFB at Week 36: Improved (n=167,170)	29.94	34.12		
CFB at Week 36: Unchanged (n=167,170)	61.08	58.24		
CFB at Week 36: Worsened (n=167,170)	8.98	7.65		
CFB at Week 52: Improved (n=154,159)	37.66	33.96		
CFB at Week 52: Unchanged (n=154,159)	50.65	56.60		
CFB at Week 52: Worsened (n=154,159)	11.69	9.43		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Participants With Change from Baseline in Patient Global Impression of Severity (PGIS) Score

End point title	Part 2: Percentage of Participants With Change from Baseline in Patient Global Impression of Severity (PGIS) Score

End point description:

PGIS of Heart Failure Symptoms is a 1-item questionnaire to assess the participant's impression of symptoms severity, specifically: shortness of breath, fatigue and swelling. The PGI-S asks the participant to choose one response that best describes how his/her heart failure symptoms, specifically: shortness of breath, fatigue and swelling are now on a 5-point scale, ranging from 'Not at all' (1) to 'Very severe' (5). C1 = none (good), C2 = mild, C3 = moderate, C4 = severe, C5 = very severe (bad). Percentage of participants by change in score are reported. Participants with change from baseline were classified as improved (shifted from higher to score), unchanged (no change in score) or worsened (shifted from lower to higher score). Participants in the full analysis set with available data were analyzed. Number analyzed is the number of participants with data available for analyses at specific timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 24, 36, and 52

End point values	Part 2: LCZ696	Part 2: Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	188		
Units: percentage of participants				
number (not applicable)				
CFB at Week 4: Improved (n=174,182)	27.01	29.67		
CFB at Week 4: Unchanged (n=174,182)	58.05	59.89		
CFB at Week 4: Worsened (n=174,182)	14.94	10.44		
CFB at Week 12: Improved (n=172,172)	30.90	31.46		

CFB at Week 12: Unchanged (n=172,172)	52.25	55.62		
CFB at Week 12: Worsened (n=172,172)	16.85	12.92		
CFB at Week 24: Improved (n=174,171)	33.33	38.01		
CFB at Week 24: Unchanged (n=174,171)	48.85	48.54		
CFB at Week 24: Worsened (n=174,171)	17.82	13.45		
CFB at Week 36: Improved (n=162,165)	33.33	33.94		
CFB at Week 36: Unchanged (n=162,165)	49.38	52.73		
CFB at Week 36: Worsened (n=162,165)	17.28	13.33		
CFB at Week 52: Improved (n=152,158)	35.53	34.81		
CFB at Week 52: Unchanged (n=152,158)	48.03	47.47		
CFB at Week 52: Worsened (n=152,158)	16.45	17.72		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 analytes: Clearance from Plasma (CL)

End point title	Part 1 and Part 2: Population PK of LCZ696 analytes: Clearance from Plasma (CL)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: L/h				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	25.93 (± 19.29)			
LBQ657 (n=202)	0.44 (± 0.31)			
Valsartan	1.97 (± 1.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 analytes: Volume of Distribution in Steady State

End point title	Part 1 and Part 2: Population PK of LCZ696 analytes: Volume of Distribution in Steady State

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: L/Kg				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	4.67 (± 5.84)			
LBQ657 (n=202)	0.34 (± 0.12)			
Valsartan	0.68 (± 0.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 Analytes: Absorption Rate Constant (Ka)

End point title	Part 1 and Part 2: Population PK of LCZ696 Analytes: Absorption Rate Constant (Ka)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1

and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: 1/hour				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	1.25 (± 0.01)			
LBQ657 (n=202)	1.04 (± 1.34)			
Valsartan	1.42 (± 0.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 Analytes: Maximum Drug Concentration in Plasma at Steady State (Cmax,ss)

End point title	Part 1 and Part 2: Population PK of LCZ696 Analytes: Maximum Drug Concentration in Plasma at Steady State (Cmax,ss)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: ng/mL				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	1348 (± 627)			
LBQ657 (n=202)	10153 (± 3591)			
Valsartan (n=203)	3861 (± 1770)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 Analytes: Time required to drug concentration to decrease by half (T 1/2)

End point title	Part 1 and Part 2: Population PK of LCZ696 Analytes: Time required to drug concentration to decrease by half (T 1/2)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: hours				
median (full range (min-max))				
Sacubitril (n=202)	8.51 (1.87 to 199.55)			
LBQ657 (n=202)	18.21 (6.08 to 107.47)			
Valsartan	7.96 (2.33 to 81.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 Analytes: Lowest Plasma Concentration Observed During a Dosing Interval at Steady State (Cmin,ss)

End point title	Part 1 and Part 2: Population PK of LCZ696 Analytes: Lowest Plasma Concentration Observed During a Dosing Interval at Steady State (Cmin,ss)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: ng/mL				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	63 (± 141)			
LBQ657 (n=202)	6442 (± 3474)			
Valsartan (n=203)	1442 (± 1564)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 and Part 2: Population PK of LCZ696 Analytes: Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau at Steady State (AUCtau,ss)

End point title	Part 1 and Part 2: Population PK of LCZ696 Analytes: Area Under the Plasma Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau at Steady State (AUCtau,ss)

End point description:

The population PK approach was used to describe the pharmacokinetics of LCZ696 analytes. The population PK analysis dataset included all participants from Part 1 and 2 for whom plasma concentrations were available. Number analyzed are participants with data available for analysis.

End point type	Secondary

End point timeframe:

Part 1: Age group 1- Pre-dose and 0.5, 1, 2, 4, 8, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Age groups 2 and 3- Pre-dose and 1, 2, 4, 10, optional 24 hours post-dose on Day 1 of Period 1 and 2; Part 2: Weeks 2, 8, 12, 52

End point values	LCZ696 (Part 1 and 2)			
Subject group type	Subject analysis set			
Number of subjects analysed	203			
Units: ng/mL*h				
arithmetic mean (standard deviation)				
Sacubitril (n=202)	2179 (± 2241)			
LBQ657 (n=202)	98906 (± 41944)			
Valsartan (n=203)	28672 (± 19686)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Part 2: Percentage of Participants with Treatment Emergent Adverse Events (TEAEs)

End point description:

An AE is any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related, that occurs after a participant provides informed consent. TEAEs during part 2 are defined as any recorded AE with its start date (recorded or imputed) later than or equal to the date of the first dose of the study drug within part 2and its start date prior to or equal to the end date of part 2. Part 2: Safety Set (SAF2) included randomized participants who received at least one dose of study drug. Participants were analyzed according to the treatment actually received. The treatment actually received was considered identical to the randomized treatment if the participant had received at least one dose of the randomized treatment.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study drug in Part 2 (up to 56 weeks)

End point values	Part 2: LCZ696	Part 2: Enalapril		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: percentage of participant				
number (not applicable)	88.77	87.77		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: From first dose to 30 days after last dose of study drug in Part 1; Part 2: From first dose to 30 days after last dose of study drug in Part 2 (up to 56 weeks)

Adverse event reporting additional description:

Part 1: Safety Set(SAF1) included participants who completed the Part 1 screening phase and received at least one dose of study drug during Part 1 of the study. Part 2:Safety Set(SAF2) included randomized participants who received at least one dose of study drug. Participants were analyzed according to the treatment actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Part 1: Dose Cohort 1

Reporting group description:

Participants received LCZ696 0.4 mg/kg (age group 3 {1 month to < 1 year}) or 0.8 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}, based on age, given as a single oral dose on Day 1 of period 1.

Reporting group title	Part 1: Dose Cohort 2

Reporting group description:

Participants received LCZ696 1.6 mg/kg (age group 3 {1 month to < 1 year}) or 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years}, based on age, given as a single oral dose on Day 1 of period 2.

Reporting group title	Part 1: Dose Cohort S

Reporting group description:

Participants in the dose cohort 2 who received LCZ696 3.1 mg/kg on Day 1 of period 2 and later received LCZ696 0.8 mg/kg, within period 2.

Reporting group title	Part 2: LCZ696

Reporting group description:

Participants received LCZ696 3.1 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years} or 2.3 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, twice a day (BID) for 52 weeks.

Reporting group title	Part 2: Enalapril

Reporting group description:

Participants received enalapril 0.2 mg/kg (age group 1 {6 to <18 years} and age group 2 {1 to < 6 years} or 0.15 mg/kg (age group 3 {1 month to < 1 year}), based on age, orally, BID, for 52 weeks.

Serious adverse events	Part 1: Dose Cohort 1	Part 1: Dose Cohort 2	Part 1: Dose Cohort S
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 17 (11.76%)	1 / 18 (5.56%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Death			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Malaise			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Sudden death			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Acute respiratory failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Asthma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Epistaxis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypoxia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Orthopnoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pulmonary oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory distress			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Tachypnoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Wheezing			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Suicidal ideation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Blood creatinine increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Blood urea increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 output decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Coronavirus test positive			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Human rhinovirus test positive			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Weight increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Accidental overdose			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Concussion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Fall			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Congenital, familial and genetic disorders			
Adrenogenital syndrome			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 disorders			
Arrhythmia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Arrhythmia supraventricular			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Atrial thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Bradycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 arrest			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 acute			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 tamponade			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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 ventricular thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Cardiomyopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Congestive cardiomyopathy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (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
Myocarditis			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pulseless electrical activity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Ventricular dysfunction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Nervous system disorders			
Akinesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Basal ganglia infarction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Brain injury			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Cerebral infarction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Encephalopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Febrile convulsion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hemiparesis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Juvenile myoclonic epilepsy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Neuromyopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Partial seizures			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Seizure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Status epilepticus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Ascites			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Gastritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Intestinal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Intussusception			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Renal artery stenosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Renal impairment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Musculoskeletal and connective tissue disorders			
Neck mass			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pathological fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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			
Appendicitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Bronchiolitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Bronchitis viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Gastroenteritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Influenza			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pneumonia influenzal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pneumonia mycoplasmal			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pneumonia viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pyelonephritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Septic shock			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Viral sepsis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (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			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Electrolyte imbalance			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Feeding intolerance			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Fluid retention			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypocalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypoglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Hypophagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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
Malnutrition			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (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

Serious adverse events	Part 2: LCZ696	Part 2: Enalapril	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 187 (36.90%)	62 / 188 (32.98%)	
number of deaths (all causes)	8	12	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 187 (2.14%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			

subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 187 (2.14%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cough			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachypnoea			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood urea increased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac output decreased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus test positive			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Concussion			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Adrenogenital syndrome			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	2 / 187 (1.07%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 4	
Cardiac disorder			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	24 / 187 (12.83%)	23 / 188 (12.23%)	
occurrences causally related to treatment / all	2 / 34	3 / 34	
deaths causally related to treatment / all	0 / 1	1 / 2	
Cardiac failure acute			
subjects affected / exposed	2 / 187 (1.07%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	4 / 187 (2.14%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac tamponade			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			

subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Akinesia			

subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia infarction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile convulsion			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Juvenile myoclonic epilepsy			

subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyopathy			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 187 (0.53%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 187 (2.67%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck mass			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (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			
Appendicitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchiolitis			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 187 (1.07%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	5 / 187 (2.67%)	4 / 188 (2.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 187 (2.14%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			

subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding intolerance			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Part 1: Dose Cohort 1	Part 1: Dose Cohort 2	Part 1: Dose Cohort S
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	10 / 18 (55.56%)	1 / 2 (50.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Face oedema			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 2 (50.00%)
occurrences (all)	0	2	2
Medical device pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cough			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Wheezing			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood uric acid increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Body temperature increased			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
SARS-CoV-2 test negative			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lip injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Arrhythmia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bradycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypersomnia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Lymphadenopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Enteritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)	4 / 18 (22.22%)	1 / 2 (50.00%)
occurrences (all)	1	4	1
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Renal impairment			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Atypical pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear infection			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Exanthema subitum			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	3 / 18 (16.67%)	1 / 2 (50.00%)
occurrences (all)	0	3	1
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 17 (0.00%)	0 / 18 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: LCZ696	Part 2: Enalapril	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	161 / 187 (86.10%)	156 / 188 (82.98%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	21 / 187 (11.23%)	22 / 188 (11.70%)	
occurrences (all)	31	36	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Chest discomfort			

subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Chest pain			
subjects affected / exposed	7 / 187 (3.74%)	7 / 188 (3.72%)	
occurrences (all)	8	10	
Face oedema			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	19 / 187 (10.16%)	14 / 188 (7.45%)	
occurrences (all)	19	19	
Medical device pain			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	4	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	7 / 187 (3.74%)	2 / 188 (1.06%)	
occurrences (all)	8	2	
Peripheral swelling			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	36 / 187 (19.25%)	34 / 188 (18.09%)	
occurrences (all)	49	50	
Swelling face			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Dysmenorrhoea			

subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	36 / 187 (19.25%)	38 / 188 (20.21%)	
occurrences (all)	57	49	
Dyspnoea			
subjects affected / exposed	6 / 187 (3.21%)	4 / 188 (2.13%)	
occurrences (all)	6	4	
Dyspnoea exertional			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	9 / 187 (4.81%)	6 / 188 (3.19%)	
occurrences (all)	11	9	
Nasal congestion			
subjects affected / exposed	3 / 187 (1.60%)	4 / 188 (2.13%)	
occurrences (all)	5	5	
Oropharyngeal pain			
subjects affected / exposed	9 / 187 (4.81%)	5 / 188 (2.66%)	
occurrences (all)	9	6	
Pneumothorax			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Productive cough			
subjects affected / exposed	5 / 187 (2.67%)	1 / 188 (0.53%)	
occurrences (all)	5	1	
Respiratory disorder			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	2	2	
Rhinitis allergic			

subjects affected / exposed	2 / 187 (1.07%)	4 / 188 (2.13%)	
occurrences (all)	2	4	
Rhinorrhoea			
subjects affected / exposed	7 / 187 (3.74%)	7 / 188 (3.72%)	
occurrences (all)	9	7	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Wheezing			
subjects affected / exposed	2 / 187 (1.07%)	2 / 188 (1.06%)	
occurrences (all)	2	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 187 (1.60%)	5 / 188 (2.66%)	
occurrences (all)	5	5	
Depression			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Insomnia			
subjects affected / exposed	4 / 187 (2.14%)	3 / 188 (1.60%)	
occurrences (all)	5	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences (all)	3	1	
Blood creatine increased			
subjects affected / exposed	0 / 187 (0.00%)	0 / 188 (0.00%)	
occurrences (all)	0	0	
Blood creatinine increased			
subjects affected / exposed	6 / 187 (3.21%)	5 / 188 (2.66%)	
occurrences (all)	6	8	
Blood potassium increased			

subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Blood urea increased			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Blood uric acid increased			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Body temperature increased			
subjects affected / exposed	0 / 187 (0.00%)	0 / 188 (0.00%)	
occurrences (all)	0	0	
Glomerular filtration rate decreased			
subjects affected / exposed	9 / 187 (4.81%)	12 / 188 (6.38%)	
occurrences (all)	10	13	
Hepatic enzyme increased			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
SARS-CoV-2 test negative			
subjects affected / exposed	6 / 187 (3.21%)	1 / 188 (0.53%)	
occurrences (all)	8	1	
Weight decreased			
subjects affected / exposed	0 / 187 (0.00%)	4 / 188 (2.13%)	
occurrences (all)	0	4	
Weight increased			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Contusion			
subjects affected / exposed	2 / 187 (1.07%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Fall			

subjects affected / exposed	2 / 187 (1.07%)	5 / 188 (2.66%)	
occurrences (all)	3	7	
Lip injury			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 187 (0.00%)	4 / 188 (2.13%)	
occurrences (all)	0	4	
Skin abrasion			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	2	3	
Skin laceration			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 187 (0.00%)	0 / 188 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences (all)	3	1	
Arrhythmia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Bradycardia			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Cardiac failure			
subjects affected / exposed	5 / 187 (2.67%)	6 / 188 (3.19%)	
occurrences (all)	6	6	
Left ventricular dysfunction			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Palpitations			

subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	4	1	
Tachycardia			
subjects affected / exposed	0 / 187 (0.00%)	4 / 188 (2.13%)	
occurrences (all)	0	5	
Ventricular extrasystoles			
subjects affected / exposed	0 / 187 (0.00%)	4 / 188 (2.13%)	
occurrences (all)	0	4	
Ventricular tachycardia			
subjects affected / exposed	2 / 187 (1.07%)	3 / 188 (1.60%)	
occurrences (all)	4	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 187 (12.30%)	15 / 188 (7.98%)	
occurrences (all)	29	22	
Headache			
subjects affected / exposed	22 / 187 (11.76%)	20 / 188 (10.64%)	
occurrences (all)	45	24	
Hypersomnia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Presyncope			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences (all)	2	5	
Syncope			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	7 / 187 (3.74%)	5 / 188 (2.66%)	
occurrences (all)	7	5	
Lymphadenopathy			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	3	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 187 (1.07%)	2 / 188 (1.06%)	
occurrences (all)	4	3	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Abdominal distension			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	15 / 187 (8.02%)	11 / 188 (5.85%)	
occurrences (all)	36	13	
Abdominal pain upper			
subjects affected / exposed	6 / 187 (3.21%)	9 / 188 (4.79%)	
occurrences (all)	7	10	
Constipation			
subjects affected / exposed	6 / 187 (3.21%)	7 / 188 (3.72%)	
occurrences (all)	12	8	
Dental caries			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	25 / 187 (13.37%)	23 / 188 (12.23%)	
occurrences (all)	35	26	
Dyspepsia			

subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Enteritis			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	2	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 187 (2.67%)	1 / 188 (0.53%)	
occurrences (all)	5	1	
Gingival bleeding			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Mouth ulceration			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	9 / 187 (4.81%)	9 / 188 (4.79%)	
occurrences (all)	9	13	
Toothache			
subjects affected / exposed	5 / 187 (2.67%)	2 / 188 (1.06%)	
occurrences (all)	5	2	
Vomiting			
subjects affected / exposed	33 / 187 (17.65%)	37 / 188 (19.68%)	
occurrences (all)	51	52	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Dermatitis allergic			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Dermatitis contact			

subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Ecchymosis			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences (all)	3	2	
Eczema			
subjects affected / exposed	4 / 187 (2.14%)	1 / 188 (0.53%)	
occurrences (all)	6	1	
Erythema			
subjects affected / exposed	4 / 187 (2.14%)	1 / 188 (0.53%)	
occurrences (all)	4	1	
Hyperhidrosis			
subjects affected / exposed	3 / 187 (1.60%)	1 / 188 (0.53%)	
occurrences (all)	3	1	
Ingrowing nail			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	3	
Petechiae			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	2 / 187 (1.07%)	3 / 188 (1.60%)	
occurrences (all)	2	3	
Rash			
subjects affected / exposed	5 / 187 (2.67%)	6 / 188 (3.19%)	
occurrences (all)	6	6	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	2	
Polyuria			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	

Renal failure			
subjects affected / exposed	1 / 187 (0.53%)	1 / 188 (0.53%)	
occurrences (all)	1	1	
Renal impairment			
subjects affected / exposed	4 / 187 (2.14%)	2 / 188 (1.06%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 187 (2.14%)	1 / 188 (0.53%)	
occurrences (all)	6	1	
Back pain			
subjects affected / exposed	6 / 187 (3.21%)	3 / 188 (1.60%)	
occurrences (all)	7	3	
Muscle spasms			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	6 / 187 (3.21%)	3 / 188 (1.60%)	
occurrences (all)	6	3	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 187 (0.00%)	3 / 188 (1.60%)	
occurrences (all)	0	3	
Atypical pneumonia			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	12 / 187 (6.42%)	8 / 188 (4.26%)	
occurrences (all)	15	11	
COVID-19			

subjects affected / exposed	6 / 187 (3.21%)	2 / 188 (1.06%)	
occurrences (all)	6	2	
Candida infection			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Ear infection			
subjects affected / exposed	2 / 187 (1.07%)	3 / 188 (1.60%)	
occurrences (all)	2	5	
Exanthema subitum			
subjects affected / exposed	2 / 187 (1.07%)	0 / 188 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	9 / 187 (4.81%)	11 / 188 (5.85%)	
occurrences (all)	11	13	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	3	3	
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 187 (1.07%)	3 / 188 (1.60%)	
occurrences (all)	2	3	
Influenza			
subjects affected / exposed	11 / 187 (5.88%)	12 / 188 (6.38%)	
occurrences (all)	15	13	
Nasopharyngitis			
subjects affected / exposed	29 / 187 (15.51%)	17 / 188 (9.04%)	
occurrences (all)	57	32	
Oral herpes			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Otitis media			
subjects affected / exposed	5 / 187 (2.67%)	3 / 188 (1.60%)	
occurrences (all)	5	3	
Otitis media acute			

subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	2	
Pharyngitis			
subjects affected / exposed	6 / 187 (3.21%)	5 / 188 (2.66%)	
occurrences (all)	7	5	
Pharyngitis streptococcal			
subjects affected / exposed	3 / 187 (1.60%)	0 / 188 (0.00%)	
occurrences (all)	3	0	
Pneumonia			
subjects affected / exposed	3 / 187 (1.60%)	3 / 188 (1.60%)	
occurrences (all)	3	3	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 187 (0.00%)	1 / 188 (0.53%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 187 (1.07%)	1 / 188 (0.53%)	
occurrences (all)	2	1	
Respiratory tract infection			
subjects affected / exposed	4 / 187 (2.14%)	5 / 188 (2.66%)	
occurrences (all)	4	5	
Rhinitis			
subjects affected / exposed	7 / 187 (3.74%)	10 / 188 (5.32%)	
occurrences (all)	12	15	
Sinusitis			
subjects affected / exposed	3 / 187 (1.60%)	2 / 188 (1.06%)	
occurrences (all)	4	2	
Tonsillitis			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Tracheitis			
subjects affected / exposed	1 / 187 (0.53%)	2 / 188 (1.06%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	37 / 187 (19.79%)	35 / 188 (18.62%)	
occurrences (all)	62	62	
Urinary tract infection			

subjects affected / exposed	1 / 187 (0.53%)	0 / 188 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	5 / 187 (2.67%)	4 / 188 (2.13%)	
occurrences (all)	5	4	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 187 (0.53%)	3 / 188 (1.60%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 187 (4.81%)	1 / 188 (0.53%)	
occurrences (all)	10	1	
Dehydration			
subjects affected / exposed	2 / 187 (1.07%)	2 / 188 (1.06%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	0 / 187 (0.00%)	2 / 188 (1.06%)	
occurrences (all)	0	2	
Hyperkalaemia			
subjects affected / exposed	6 / 187 (3.21%)	6 / 188 (3.19%)	
occurrences (all)	7	8	
Hypokalaemia			
subjects affected / exposed	4 / 187 (2.14%)	1 / 188 (0.53%)	
occurrences (all)	4	1	
Iron deficiency			
subjects affected / exposed	0 / 187 (0.00%)	3 / 188 (1.60%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	The following changes were made in amendment 1: - Added second dose to Part 1 study design and other relevant sections. Assessment schedule, Safety, pharmacokinetic (PK), and pharmacodynamic (PD) data review have been revised accordingly. - Total of six participants per dose for each age group is planned. Two doses are being assessed in Groups 1 and 2, and one dose is being assessed in Group 3. - For the PedsQL scale, the chronic version (one month recall period) was replaced with the acute version (7 days recall period). The reason for this change is that the patient reported assessment of 7 days is considered more appropriate compared to 1 month for pediatric heart failure patients. Added text indicating that the PedsQL Physical Functioning module will be used for the primary Global Rank endpoint only for Group 1 (6 to <18 years old). - Added safety and tolerability Secondary objective in Part 1.
10 July 2017	The following changes were made in amendment 2: - Total of six participants per dose for each age group is planned. Two doses are being assessed in Groups 1 and 2, and one dose is being assessed in Group 3. Updated and corrected blood volumes for PK and PD sampling in Part 1.
01 October 2018	The following changes were made in amendment 3: - For Part 1 Group 3 participants, removed the single dose level of LCZ696 0.8 mg/kg and replaced it with two dose levels: LCZ696 0.4 mg/kg and LCZ696 1.6 mg/kg. Inclusion criterion 7 has been modified accordingly. Total of approximately 4 observations per dose (approximately 8 in total) and a minimum of 4 participants is planned for Group 3 in Part 1. - Added to Part 2 of the study, a steady-state Sparse PK blood collection visit, applicable to a subset of participants in Group 2 (approximately 24 participants of whom approximately 12 participants are expected to be randomized to LCZ696) who agree to participate. These participants will also have NTproBNP collected at the time of the Sparse PK visit.
04 February 2019	The following changes were made in amendment 4: - Data Analysis Section: added the interim biomarker analysis.
18 September 2020	The following changes were made in amendment 5: - Added target dose level (Dose Level 4x) for Age Group 3. Added statement enabling Age Group 3 participants that turn 1 year old during the study, to be up-titrated to Group 3 Dose Level 5x (LCZ696 3.1 mg/kg bid/ enalapril 0.2 mg/kg bid). Data Analysis Section: Clarified age groups for Part 1 analysis. Added modified age groups for Part 2 analysis. - Removed enrollment target of 25% Angiotensin converting enzyme inhibitor (ACEI/ARB) naïve participants. Removed requirement for 20% of the total n of 360 (72 participants) to be randomized and included for analysis in each age group. Removed required number of participants (80) with an event in Category 1 or 2 (in two places in this section). Clarified Part 1 age groups. Clarified target dose for Age Groups 1 and 2 (Dose Level 4) and added target dose level (Dose Level 4x) for Age Group 3. Modified Tables 3-4, 3-5 and 3-6. Added safety monitoring requirements for Part 2 Age Group 3 participants. Added details enabling Age Group 3 participants that turn 1 year old during the study, to be up-titrated to Group 3 Dose Level 5x (LCZ696 3.1 mg/kg bid/ enalapril 0.2 mg/kg bid). Also added a statement indicating that a scheduled or unscheduled visit may be used for these up-titrations and added detailed criteria for up-titration. Note: References to dose levels 1 through 4 throughout the protocol have been changed to dose levels 1x to 4x for Age Group 3 participants.

08 October 2020	The following changes were made in amendment 6: - Total daily dose levels of commonly prescribed ACEI/ARBs to guide selection of the study medication starting dose: Clarified “low” and “higher” ACEI/ARB doses in the text. Removed dose levels 1x through 4x of commonly prescribed ACEI/ARBs. Part 2 (Efficacy) Study drug dose levels for double-blind enalapril and LCZ696 for age group 3: The enalapril dose for Dose Level 2x has been corrected to 0.075 mg/kg bid.
26 October 2021	The following changes were made in amendment 7: - Urgent safety measure (USM): Details regarding the USM, instructions for participants impacted by the USM and USM implications regarding data collection and study results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported