Clinical trial results:
A multicenter study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319

Summary

EudraCT number	2018-004154-25
Trial protocol	PL FR BG PT CZ ES HU HR DE AT IT FI
Global end of trial date	29 December 2023

Results information

Result version number	v1 (current)
This version publication date	06 July 2024
First version publication date	06 July 2024

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2319E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03785405
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG , 42 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG , 42 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To further evaluate long-term safety and tolerability of sacubitril/valsartan in eligible PANORAMA-HF participants receiving open-label sacubitril/valsartan

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 10
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Lebanon: 9
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Russian Federation: 3

Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Türkiye: 11
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	215
EEA total number of subjects	72

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)	6
Children (2-11 years)	127
Adolescents (12-17 years)	66
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

79 centers in 27 countries: Korea, Republic of, United States, Bulgaria, Italy, Thailand, Poland, Japan, Singapore, Israel, Turkey, Taiwan, South Africa, Portugal, Lebanon, Canada(2), Switzerland, Czech Republic, Croatia, Argentina, Hungary, India, Germany, France, Austria, Spain, Russia, Finland

Pre-assignment

Screening details:

A 36-hour washout after the last dose of study medication taken in the PANORAMA-HF core study (Visit 416) was required for all participants before starting Open Label Extension study medication.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Age Group 1

Arm description:

Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid

Arm type	Experimental
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

sacubitril/valsartan 200mg bid

Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

sacubitril/valsartan 200mg bid

Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	lCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

sacubitril/valsartan 200mg bid

Arm title	Age Group 2

Arm description:

Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid

Arm type	Experimental

Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: sacubitril/valsartan 200mg bid	
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use
Dosage and administration details: sacubitril/valsartan 200mg bid	
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: sacubitril/valsartan 200mg bid	

Number of subjects in period 1	Age Group 1	Age Group 2
Started	130	85
Completed	92	74
Not completed	38	11
Adverse event, serious fatal	6	4
Physician decision	8	5
Participant decision	2	-
Not available	1	-
Adverse event, non-fatal	16	1
Lost to follow-up	1	-
Guardian decision	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Age Group 1
Reporting group description:	
Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid	
Reporting group title	Age Group 2
Reporting group description:	
Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid	

Reporting group values	Age Group 1	Age Group 2	Total
Number of subjects	130	85	215
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	6	6
Children (2-11 years)	48	79	127
Adolescents (12-17 years)	66	0	66
Adults (18-64 years)	16	0	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	12.83	2.94	
standard deviation	± 3.864	± 1.149	-
Sex: Female, Male Units: Participants			
Female	60	49	109
Male	70	36	106
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	2	0	2
White	78	41	119
Asian	24	23	47
Black or African American	19	10	29
Multiple	0	4	4
Native Hawaiian or Other Pacific Islander	0	1	1
Unknown	7	6	13

End points

End points reporting groups

Reporting group title	Age Group 1
Reporting group description:	
Patients 6 years and older receiving open label sacubitril/valsartan 3.1 mg/kg bid	
Reporting group title	Age Group 2
Reporting group description:	
Patients 1 year to < 6 years receiving open label sacubitril/valsartan 3.1 mg/kg bid	

Primary: Duration of drug exposure

End point title	Duration of drug exposure[1]
End point description:	
Median duration of exposure to sacubitril/valsartan (including temporary interruptions)	
End point type	Primary
End point timeframe:	
Up to 4.5 years	

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 statistical analysis was planned for this primary outcome.

End point values	Age Group 1	Age Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	85		
Units: Days				
median (full range (min-max))	894 (23 to 1612)	951 (62 to 1570)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Serious Adverse Events

End point title	Number of participants with Serious Adverse Events[2]
End point description:	
Number of participants with at least one Serious Adverse Events (SAEs)	
End point type	Primary
End point timeframe:	
to end of study, up to 4.5 years	

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 statistical analysis was planned for this primary outcome.

End point values	Age Group 1	Age Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	85		
Units: Participants	59	25		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Adverse Events

End point title	Number of participants with Adverse Events[3]

End point description:

Number of participants with at least one Adverse Events (AEs)

End point type	Primary

End point timeframe:

to end of study, up to 4,5 years

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 statistical analysis was planned for this primary outcome.

End point values	Age Group 1	Age Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	85		
Units: Participants	111	78		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from fi rst dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 4.5 years

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifi cations, Novartis has reported under the Serious adverse events fi eld "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Age group 1 (6 Years or more)

Reporting group description:

Age group 1 (6 Years or more)

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Age group 2 (1 to less than 6 years)

Reporting group description:

Age group 2 (1 to less than 6 years)

Serious adverse events	Age group 1 (6 Years or more)	Total	Age group 2 (1 to less than 6 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 130 (45.38%)	84 / 215 (39.07%)	25 / 85 (29.41%)
number of deaths (all causes)	7	11	4
number of deaths resulting from adverse events	1	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 130 (2.31%)	4 / 215 (1.86%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	1 / 3	2 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 130 (2.31%)	6 / 215 (2.79%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site pain			

subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site extravasation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	5 / 130 (3.85%)	5 / 215 (2.33%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 130 (2.31%)	3 / 215 (1.40%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atelectasis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Product issues			
Device malfunction			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device power source issue			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcus test positive			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus test positive			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incorrect dose administered			

subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital epiblepharon			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure			
subjects affected / exposed	15 / 130 (11.54%)	18 / 215 (8.37%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	1 / 24	2 / 30	1 / 6
deaths causally related to treatment / all	1 / 3	1 / 5	0 / 2
Cardiac failure chronic			
subjects affected / exposed	4 / 130 (3.08%)	6 / 215 (2.79%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure acute			
subjects affected / exposed	2 / 130 (1.54%)	4 / 215 (1.86%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dilated cardiomyopathy			
subjects affected / exposed	5 / 130 (3.85%)	5 / 215 (2.33%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary valve stenosis			

subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia induced cardiomyopathy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 130 (1.54%)	3 / 215 (1.40%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular dysfunction			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenic cyst			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 130 (2.31%)	5 / 215 (2.33%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 130 (2.31%)	3 / 215 (1.40%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal impairment			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc space narrowing			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)	2 / 215 (0.93%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	4 / 130 (3.08%)	6 / 215 (2.79%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	2 / 130 (1.54%)	2 / 215 (0.93%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
COVID-19			
subjects affected / exposed	4 / 130 (3.08%)	8 / 215 (3.72%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	5 / 130 (3.85%)	9 / 215 (4.19%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	0 / 8	0 / 12	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypernatraemia			

subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 130 (0.77%)	2 / 215 (0.93%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 215 (0.47%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 130 (0.77%)	1 / 215 (0.47%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Age group 1 (6 Years or more)	Total	Age group 2 (1 to less than 6 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 130 (69.23%)	150 / 215 (69.77%)	60 / 85 (70.59%)
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	13 / 130 (10.00%)	14 / 215 (6.51%)	1 / 85 (1.18%)
occurrences (all)	16	17	1
Vascular disorders			

Hypotension			
subjects affected / exposed	18 / 130 (13.85%)	21 / 215 (9.77%)	3 / 85 (3.53%)
occurrences (all)	26	29	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 130 (10.77%)	14 / 215 (6.51%)	0 / 85 (0.00%)
occurrences (all)	23	23	0
Headache			
subjects affected / exposed	15 / 130 (11.54%)	18 / 215 (8.37%)	3 / 85 (3.53%)
occurrences (all)	21	24	3
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 130 (11.54%)	37 / 215 (17.21%)	22 / 85 (25.88%)
occurrences (all)	23	56	33
Chest pain			
subjects affected / exposed	8 / 130 (6.15%)	10 / 215 (4.65%)	2 / 85 (2.35%)
occurrences (all)	11	13	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 130 (6.92%)	18 / 215 (8.37%)	9 / 85 (10.59%)
occurrences (all)	17	28	11
Abdominal pain			
subjects affected / exposed	10 / 130 (7.69%)	13 / 215 (6.05%)	3 / 85 (3.53%)
occurrences (all)	12	15	3
Vomiting			
subjects affected / exposed	15 / 130 (11.54%)	27 / 215 (12.56%)	12 / 85 (14.12%)
occurrences (all)	20	44	24
Nausea			
subjects affected / exposed	9 / 130 (6.92%)	10 / 215 (4.65%)	1 / 85 (1.18%)
occurrences (all)	9	10	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	6 / 130 (4.62%)	12 / 215 (5.58%)	6 / 85 (7.06%)
occurrences (all)	8	19	11
Oropharyngeal pain			

subjects affected / exposed	7 / 130 (5.38%)	9 / 215 (4.19%)	2 / 85 (2.35%)
occurrences (all)	8	15	7
Dyspnoea			
subjects affected / exposed	10 / 130 (7.69%)	10 / 215 (4.65%)	0 / 85 (0.00%)
occurrences (all)	12	12	0
Cough			
subjects affected / exposed	20 / 130 (15.38%)	39 / 215 (18.14%)	19 / 85 (22.35%)
occurrences (all)	27	58	31
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	8 / 130 (6.15%)	10 / 215 (4.65%)	2 / 85 (2.35%)
occurrences (all)	8	10	2
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	7 / 130 (5.38%)	14 / 215 (6.51%)	7 / 85 (8.24%)
occurrences (all)	8	20	12
Influenza			
subjects affected / exposed	6 / 130 (4.62%)	14 / 215 (6.51%)	8 / 85 (9.41%)
occurrences (all)	8	20	12
Conjunctivitis			
subjects affected / exposed	3 / 130 (2.31%)	8 / 215 (3.72%)	5 / 85 (5.88%)
occurrences (all)	4	14	10
COVID-19			
subjects affected / exposed	23 / 130 (17.69%)	47 / 215 (21.86%)	24 / 85 (28.24%)
occurrences (all)	25	51	26
Nasopharyngitis			
subjects affected / exposed	12 / 130 (9.23%)	26 / 215 (12.09%)	14 / 85 (16.47%)
occurrences (all)	21	78	57
Upper respiratory tract infection			
subjects affected / exposed	8 / 130 (6.15%)	30 / 215 (13.95%)	22 / 85 (25.88%)
occurrences (all)	15	57	42
Pharyngitis			
subjects affected / exposed	6 / 130 (4.62%)	11 / 215 (5.12%)	5 / 85 (5.88%)
occurrences (all)	7	14	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2021	The primary purpose of this protocol amendment was to extend the duration of the study. The original protocol was expected to end as early as May-2022 and no later than Dec-2022. In this amendment, the duration of the study was extended to ensure that study participants continued to receive age-appropriate study drug treatment (especially those requiring the pediatric formulations not currently available outside investigational use) and safety follow-up until the expected time when pediatric use of sacubitril/valsartan received local marketing authorization and became commercially available to participants.
30 November 2021	On 26-Oct-2021, an urgent safety measure (USM) was implemented by Novartis in the PANORAMA-HF core study due to a quality issue with enalapril, the active comparator. The USM included the following: • Investigational medicinal product (IMP) dispensation was blocked in the IRT system by Novartis • All participants who were receiving study medication at the time the USM was initiated, had to discontinue study treatment by 31-Oct-2021 and change to local standard of care, respecting any required washout periods. These participants were to attend an unscheduled visit at the site by 31-Oct-2021, or as soon as possible thereafter, for safety and efficacy assessments. • It was requested for all patients to return IMP in their possession by 31-Oct-2021. • All IMP is to be removed from the sites for destruction per local practices. As a result, not all the participants were on study drug treatment at PANORAMAHF Part 2 EOS visit (Visit 416). The purpose of the second protocol amendment was to amend the inclusion and exclusion criteria to allow participants impacted by the USM to enroll into this OLE study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported