Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRIBUTE-CM Trial)

Summary

EudraCT number	2018-004280-32
Trial protocol	GB DK IE PT ES NL BE HU PL GR IT
Global end of trial date	11 May 2023

Results information

Result version number	v1 (current)
This version publication date	26 May 2024
First version publication date	26 May 2024

Trial information

Trial identification

Sponsor protocol code	AG10-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03860935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eidos Therapeutics, Inc.
Sponsor organisation address	1800 Owens St., Ste C-1200, San Francisco, CA 94158, United States,
Public contact	VP, Clinical Operations , Eidos Therapeutics Inc., a BridgeBio Company, 001 415-887-1471, Mark.McGovern@bridgebio.com
Scientific contact	VP, Clinical Development , Eidos Therapeutics Inc., a BridgeBio Company, 001 415-887-1471, JF.Tamby@bridgebio.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of acoramidis in the treatment of participants with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM) by evaluating the difference between the acoramidis and placebo groups in the combined endpoints of All-Cause Mortality, the cumulative frequency of cardiovascular (CV)-related hospitalization, change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP), and change from baseline in 6-Minute Walk Test (6MWT).

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with the ICH GCP guidelines, US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive (and Clinical Trial Regulation when in effect); principles enunciated in the Declaration of Helsinki; and all human clinical research regulations of the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2019
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	United States: 126
Country: Number of subjects enrolled	Australia: 71
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	New Zealand: 28
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	Denmark: 43
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Ireland: 6

Country: Number of subjects enrolled	Italy: 68
Worldwide total number of subjects	632
EEA total number of subjects	258

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	544
85 years and over	67

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 95 centers in 18 countries between April 2019 and May 2023.

Pre-assignment

Screening details:

The study included a Screening Period of up to 35 days, a fixed treatment duration of 30 months, and a 1-month follow-up after the last dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Acoramidis HCl 800 mg

Arm description:

Participants with symptomatic ATTR-CM received 800 mg acoramidis HCl BID (two 400 mg acoramidis HCl tablets, each equivalent to 356 mg acoramidis [active moiety])

Arm type	Experimental
Investigational medicinal product name	Acoramidis
Investigational medicinal product code	
Other name	AG10
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally BID.

Arm title	Placebo

Arm description:

Participants with symptomatic ATTR-CM received matching placebo (two matching placebo tablets BID)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally BID.

Number of subjects in period 1	Acoramidis HCl 800 mg	Placebo
Started	421	211
Completed	331	154
Not completed	90	57
Consent withdrawn by subject	15	6
Death	75	51

Baseline characteristics

Reporting groups	
Reporting group title	Acoramidis HCl 800 mg
Reporting group description:	
Participants with symptomatic ATTR-CM received 800 mg acoramidis HCl BID (two 400 mg acoramidis HCl tablets, each equivalent to 356 mg acoramidis [active moiety])	
Reporting group title	Placebo
Reporting group description:	
Participants with symptomatic ATTR-CM received matching placebo (two matching placebo tablets BID)	

Reporting group values	Acoramidis HCl 800 mg	Placebo	Total
Number of subjects	421	211	632
Age categorical Units: Subjects			
Adults (18-64 years)	12	9	21
Adults (65-77)	190	95	285
Adults (≥78)	219	107	326
Age continuous Units: years			
arithmetic mean	77.37	77.09	
standard deviation	± 6.450	± 6.763	-
Gender categorical Units: Subjects			
Female	37	25	62
Male	384	186	570
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	4	12
Not Hispanic or Latino	401	199	600
Unknown or Not Reported	12	8	20
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	10	3	13
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	20	10	30
White	368	187	555
More than one race	2	0	2
Unknown or Not Reported	21	9	30

End points

End points reporting groups

Reporting group title	Acoramidis HCl 800 mg
Reporting group description:	
Participants with symptomatic ATTR-CM received 800 mg acoramidis HCl BID (two 400 mg acoramidis HCl tablets, each equivalent to 356 mg acoramidis [active moiety])	
Reporting group title	Placebo
Reporting group description:	
Participants with symptomatic ATTR-CM received matching placebo (two matching placebo tablets BID)	

Primary: A Hierarchical Combination of All-Cause Mortality, Cumulative Frequency of CV-related Hospitalization, Change From Baseline in NT-proBNP and Change From Baseline in 6MWT at the Last Available Visit Where Both Subjects Had Non-missing Assessments.

End point title	A Hierarchical Combination of All-Cause Mortality, Cumulative Frequency of CV-related Hospitalization, Change From Baseline in NT-proBNP and Change From Baseline in 6MWT at the Last Available Visit Where Both Subjects Had Non-missing Assessments.

End point description:

The Finkelstein-Schoenfeld method combines all-cause mortality, cumulative frequency of CV-related hospitalizations, change from baseline in NT-proBNP and change from baseline in 6MWT in a hierarchical fashion. It compares every participant with every other participant within strata, assigning a +1 to the "better" participant and a -1 to the "worse" participant and 0 if they are "tied". Participants who had heart transplantation or implantation of a cardiac mechanical assist device were handled in the same manner as death. 'Win' represents a participant doing better based on hierarchical comparison. The reported unit is the total percent of "wins" for each treatment group from performing such a hierarchical comparison across stratification factors in the study.

The mITT population is a subset of ITT subjects which includes all randomized subjects who received at least 1 dose of IMP & have at least 1 post baseline efficacy assessment as well as a baseline eGFR >= 30 mL/min/1.73 m^2.

End point type	Primary
End point timeframe:	
Baseline up to Month 30	

End point values	Acoramidis HCl 800 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	409	202		
Units: Percent of Wins from Win Ratio				
number (not applicable)	63.7	35.9		

Statistical analyses

Statistical analysis title	Finkelstein-Schoenfeld (F-S) Analysis

Statistical analysis description:

Finkelstein-Schoenfeld (F-S) Analysis for Hierarchical Combination of All-Cause Mortality, cumulative frequency of CV-related Hospitalization, change from baseline in NT-proBNP and change from baseline in 6MWT.

Comparison groups	Placebo v Acoramidis HCl 800 mg
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Finkelstein-Schoenfeld Method

Secondary: Change From Baseline to Month 30 in the Distance Walked During the 6 Minute Walk Test (6MWT)

End point title	Change From Baseline to Month 30 in the Distance Walked During the 6 Minute Walk Test (6MWT)

End point description:

6MWT measures the total distance that a participant could walk in 6 minutes. Participants were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed.

The mITT population is a subset of ITT subjects which includes all randomized subjects who received at least 1 dose of IMP & have at least 1 post baseline efficacy assessment as well as a baseline eGFR >= 30 mL/min/1.73 m^2.

End point type	Secondary

End point timeframe:

Month 30

End point values	Acoramidis HCl 800 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	407	202		
Units: Meter				
least squares mean (standard error)	-64.65 (± 5.508)	-104.29 (± 7.772)		

Statistical analyses

Statistical analysis title	Mixed Effects Model with Repeated Measures

Statistical analysis description:

LS means are from a MMRM model with treatment group, visit, randomization stratification factors of genotype, NT-proBNP level and eGFR level (as recorded in IXRS) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study treatment and due to death were imputed using the Jump to Reference (J2R) method and sampling with replacement from the worst 5% of observed values, respectively, as specified in study SAP.

Comparison groups	Acoramidis HCl 800 mg v Placebo

Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	39.64
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	20.18
upper limit	59.1
Variability estimate	Standard error of the mean
Dispersion value	9.477

Secondary: Change From Baseline to Month 30 of the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)

End point title	Change From Baseline to Month 30 of the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)

End point description:

KCCQ is a 23-item participant-completed questionnaire that assesses health status and health-related quality of life in participants with heart failure. Eight domain scores were calculated for the KCCQ: Physical limitation, Social limitation, Quality of life, Self-efficacy, Symptom stability, Symptom frequency, Symptom burden, and Total symptoms (calculated as the mean of Symptom frequency and Symptom burden scores). The summary score of Overall Summary (calculated as mean of Physical limitation, Social limitation, Total symptoms, and Quality of life scores) was calculated. Domain and summary scores were scaled to range from 0 (minimum) to 100 (maximum); higher scores represent better health status.

The mITT population is a subset of ITT subjects which includes all randomized subjects who received at least 1 dose of IMP & have at least 1 post baseline efficacy assessment as well as a baseline eGFR >= 30 mL/min/1.73 m^2.

End point type	Secondary

End point timeframe:

Month 30

End point values	Acoramidis HCl 800 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	408	202		
Units: Score on a scale				
least squares mean (standard error)	-11.48 (± 1.181)	-21.42 (± 1.651)		

Statistical analyses

Statistical analysis title	Mixed Effects Model with Repeated Measures

Statistical analysis description:

LS means are from a MMRM model with treatment group, visit, randomization stratification factors of genotype, NT-proBNP level and eGFR level (as recorded in IXRS) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study treatment and due to death were imputed using the Jump to Reference (J2R) method and sampling with replacement from the worst 5% of observed values, respectively, as specified in study SAP.

Comparison groups	Acoramidis HCl 800 mg v Placebo
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	9.94
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	5.79
upper limit	14.1
Variability estimate	Standard error of the mean
Dispersion value	2.024

Secondary: Change From Baseline to Month 30 in Serum TTR (Prealbumin) Level

End point title	Change From Baseline to Month 30 in Serum TTR (Prealbumin) Level

End point description:

Serum TTR (Prealbumin) is an in vivo biomarker of stabilization.

The mITT population is a subset of ITT subjects which includes all randomized subjects who received at least 1 dose of IMP & have at least 1 post baseline efficacy assessment as well as a baseline eGFR >= 30 mL/min/1.73 m^2.

End point type	Secondary

End point timeframe:

Month 30

End point values	Acoramidis HCl 800 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	199		
Units: mg/dL				
least squares mean (standard error)	5.78 (± 0.391)	-1.32 (± 0.541)		

Statistical analyses

Statistical analysis title	Mixed Effects Model with Repeated Measures

Statistical analysis description:

LS means are from a MMRM model with treatment group, visit, randomization stratification factors of genotype, NT-proBNP level and eGFR level (as recorded in IXRS) and treatment group-by-visit interaction as factors, and baseline value as covariate. Missing measurements due to early discontinuation of study treatment and due to death were imputed using the Jump to Reference (J2R) method and sampling with replacement from the worst 5% of observed values, respectively, as specified in study SAP.

Comparison groups	Acoramidis HCl 800 mg v Placebo
Number of subjects included in analysis	605
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	7.1
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	5.73
upper limit	8.46
Variability estimate	Standard error of the mean
Dispersion value	0.665

Secondary: All-cause Mortality by Month 30, Including Death Due to Any Cause, Heart Transplant or Cardiac Mechanical Assist Device (CMAD)

End point title	All-cause Mortality by Month 30, Including Death Due to Any Cause, Heart Transplant or Cardiac Mechanical Assist Device (CMAD)

End point description:

Number of deaths due to any cause was analyzed. Participants who had heart transplantation or implantation of a CMAD were handled in the same manner as death.

The mITT population is a subset of ITT subjects which includes all randomized subjects who received at least 1 dose of IMP & have at least 1 post baseline efficacy assessment as well as a baseline eGFR >= 30 mL/min/1.73 m^2.

End point type	Secondary

End point timeframe:

Baseline up to Month 30

End point values	Acoramidis HCl 800 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	409	202		
Units: Participants	79	52		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	Acoramidis HCl 800 mg v Placebo
Number of subjects included in analysis	611
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0569
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Cochran-Mantel-Haenszel test is stratified by randomization stratification factors of genotype, NT-proBNP level and eGFR level as recorded in IXRS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) are events (a) with onset after first dose of study drug, or (b) present before first dose but increased in severity after, and (c) with onset <= 30 days after last dose or until first dose in extension study.

Adverse event reporting additional description:

TEAEs are any untoward or unfavorable medical occurrence in a participant, whether or not considered related to the participant's participation in the research, with event onset dates or increase in severity date as defined in the Time Frame Section above.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Acoramidis HCl 800 mg

Reporting group description:

Participants with symptomatic ATTR-CM received 800 mg acoramidis HCl BID (two 400 mg acoramidis HCl tablets, each equivalent to 356 mg acoramidis [active moiety]. Number of deaths (all causes) is based upon 30 months. Number of deaths resulting from adverse events is referent to the TEAE timeframe only.

Reporting group title	Placebo

Reporting group description:

Participants with symptomatic ATTR-CM received matching placebo BID, orally (two matching placebo tablets, BID). Number of deaths (all causes) is based upon 30 months. Number of deaths resulting from adverse events is referent to the TEAE timeframe only.

Serious adverse events	Acoramidis HCl 800 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	230 / 421 (54.63%)	137 / 211 (64.93%)	
number of deaths (all causes)	84	55	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder cancer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 421 (0.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal cancer metastatic			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma recurrent			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medullary thyroid cancer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine adenocarcinoma			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer metastatic			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transitional cell carcinoma			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Varicose vein ruptured			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	3 / 421 (0.71%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	3 / 421 (0.71%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	1 / 421 (0.24%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 421 (0.71%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Disease progression			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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			
Amyloidosis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 421 (0.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 421 (0.48%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 421 (0.48%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 421 (0.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			

Bipolar disorder			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device loosening			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lead dislodgement			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac output decreased			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
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 overdose			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back injury			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis radiation			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eschar			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	13 / 421 (3.09%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 13	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	4 / 421 (0.95%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria traumatic			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			

subjects affected / exposed	1 / 421 (0.24%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	5 / 421 (1.19%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	5 / 421 (1.19%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	19 / 421 (4.51%)	15 / 211 (7.11%)	
occurrences causally related to treatment / all	0 / 19	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 421 (0.71%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	8 / 421 (1.90%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bifascicular block			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	45 / 421 (10.69%)	39 / 211 (18.48%)	
occurrences causally related to treatment / all	0 / 64	0 / 77	
deaths causally related to treatment / all	0 / 18	0 / 8	
Cardiac amyloidosis			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac arrest			
subjects affected / exposed	4 / 421 (0.95%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure acute			
subjects affected / exposed	21 / 421 (4.99%)	14 / 211 (6.64%)	
occurrences causally related to treatment / all	1 / 28	0 / 19	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	6 / 421 (1.43%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	5 / 421 (1.19%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac flutter			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
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	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 421 (0.24%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	3 / 421 (0.71%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Chronic left ventricular failure			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 421 (0.24%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sinus node dysfunction			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	6 / 421 (1.43%)	5 / 211 (2.37%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	3 / 421 (0.71%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 421 (0.71%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chorea			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve paralysis			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Presyncope			
subjects affected / exposed	5 / 421 (1.19%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			

subjects affected / exposed	6 / 421 (1.43%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 421 (1.66%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
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	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 421 (0.71%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	6 / 421 (1.43%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal metaplasia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 421 (0.48%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 421 (0.95%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema asteatotic			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura senile			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Telangiectasia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	21 / 421 (4.99%)	8 / 211 (3.79%)	
occurrences causally related to treatment / all	0 / 21	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
End stage renal disease			

subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haematuria			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 421 (0.24%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 421 (0.24%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 421 (0.71%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	7 / 421 (1.66%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			

subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	9 / 421 (2.14%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 421 (0.48%)	8 / 211 (3.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cholecystitis infective			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective tenosynovitis			

subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 421 (0.71%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 421 (2.85%)	6 / 211 (2.84%)	
occurrences causally related to treatment / all	0 / 13	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 421 (0.95%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis pasteurella			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis streptococcal			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	4 / 421 (0.95%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin graft infection			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 421 (0.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 421 (0.48%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	7 / 421 (1.66%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 421 (0.48%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	4 / 421 (0.95%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (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	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	3 / 421 (0.71%)	5 / 211 (2.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Acoramidis HCl 800 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	410 / 421 (97.39%)	199 / 211 (94.31%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	15 / 421 (3.56%)	12 / 211 (5.69%)	
occurrences (all)	15	12	
Vascular disorders			
Hypotension			
subjects affected / exposed	30 / 421 (7.13%)	14 / 211 (6.64%)	
occurrences (all)	33	14	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	21 / 421 (4.99%)	8 / 211 (3.79%)	
occurrences (all)	22	8	
Fatigue			
subjects affected / exposed	42 / 421 (9.98%)	26 / 211 (12.32%)	
occurrences (all)	47	28	
Oedema peripheral			
subjects affected / exposed	33 / 421 (7.84%)	25 / 211 (11.85%)	
occurrences (all)	36	28	
Peripheral swelling			
subjects affected / exposed	6 / 421 (1.43%)	14 / 211 (6.64%)	
occurrences (all)	6	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 421 (7.60%)	18 / 211 (8.53%)	
occurrences (all)	37	20	
Dyspnoea			
subjects affected / exposed	51 / 421 (12.11%)	37 / 211 (17.54%)	
occurrences (all)	60	53	
Epistaxis			
subjects affected / exposed	21 / 421 (4.99%)	7 / 211 (3.32%)	
occurrences (all)	24	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	20 / 421 (4.75%)	15 / 211 (7.11%)	
occurrences (all)	21	15	
Investigations			
Blood creatinine increased			
subjects affected / exposed	26 / 421 (6.18%)	4 / 211 (1.90%)	
occurrences (all)	29	5	
Weight decreased			
subjects affected / exposed	16 / 421 (3.80%)	13 / 211 (6.16%)	
occurrences (all)	17	13	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	59 / 421 (14.01%)	38 / 211 (18.01%)	
occurrences (all)	83	60	
Skin laceration			
subjects affected / exposed	11 / 421 (2.61%)	11 / 211 (5.21%)	
occurrences (all)	15	13	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	55 / 421 (13.06%)	36 / 211 (17.06%)	
occurrences (all)	58	41	
Cardiac failure			
subjects affected / exposed	69 / 421 (16.39%)	61 / 211 (28.91%)	
occurrences (all)	103	89	
Ventricular tachycardia			
subjects affected / exposed	12 / 421 (2.85%)	12 / 211 (5.69%)	
occurrences (all)	14	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	45 / 421 (10.69%)	22 / 211 (10.43%)	
occurrences (all)	54	23	
Syncope			
subjects affected / exposed	15 / 421 (3.56%)	12 / 211 (5.69%)	
occurrences (all)	17	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	33 / 421 (7.84%)	15 / 211 (7.11%)	
occurrences (all)	36	15	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	22 / 421 (5.23%)	3 / 211 (1.42%)	
occurrences (all)	22	5	
Constipation			
subjects affected / exposed	51 / 421 (12.11%)	31 / 211 (14.69%)	
occurrences (all)	55	36	
Diarrhoea			
subjects affected / exposed	48 / 421 (11.40%)	16 / 211 (7.58%)	
occurrences (all)	55	17	
Nausea			

subjects affected / exposed	24 / 421 (5.70%)	11 / 211 (5.21%)	
occurrences (all)	26	11	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	25 / 421 (5.94%)	8 / 211 (3.79%)	
occurrences (all)	27	11	
Rash			
subjects affected / exposed	21 / 421 (4.99%)	11 / 211 (5.21%)	
occurrences (all)	24	13	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	35 / 421 (8.31%)	16 / 211 (7.58%)	
occurrences (all)	43	22	
Haematuria			
subjects affected / exposed	17 / 421 (4.04%)	16 / 211 (7.58%)	
occurrences (all)	19	18	
Renal impairment			
subjects affected / exposed	35 / 421 (8.31%)	17 / 211 (8.06%)	
occurrences (all)	39	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 421 (11.16%)	22 / 211 (10.43%)	
occurrences (all)	61	31	
Back pain			
subjects affected / exposed	38 / 421 (9.03%)	14 / 211 (6.64%)	
occurrences (all)	42	15	
Muscle spasms			
subjects affected / exposed	34 / 421 (8.08%)	15 / 211 (7.11%)	
occurrences (all)	42	15	
Pain in extremity			
subjects affected / exposed	30 / 421 (7.13%)	11 / 211 (5.21%)	
occurrences (all)	40	15	
Infections and infestations			
COVID-19			
subjects affected / exposed	80 / 421 (19.00%)	27 / 211 (12.80%)	
occurrences (all)	80	28	

Nasopharyngitis			
subjects affected / exposed	21 / 421 (4.99%)	11 / 211 (5.21%)	
occurrences (all)	23	12	
Upper respiratory tract infection			
subjects affected / exposed	22 / 421 (5.23%)	12 / 211 (5.69%)	
occurrences (all)	24	12	
Urinary tract infection			
subjects affected / exposed	46 / 421 (10.93%)	26 / 211 (12.32%)	
occurrences (all)	54	31	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 421 (4.51%)	11 / 211 (5.21%)	
occurrences (all)	21	11	
Gout			
subjects affected / exposed	46 / 421 (10.93%)	17 / 211 (8.06%)	
occurrences (all)	66	23	
Hypervolaemia			
subjects affected / exposed	21 / 421 (4.99%)	17 / 211 (8.06%)	
occurrences (all)	30	19	
Hypokalaemia			
subjects affected / exposed	21 / 421 (4.99%)	11 / 211 (5.21%)	
occurrences (all)	25	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2019	− Clarified contraception requirements and acceptable methods. − Circulatory biomarkers: changes in NT-proBNP and TnI between baseline and Month 30. − Change from baseline after 30 months of treatment in EQ-5D-5L.
28 August 2019	− Circulatory biomarkers and EQ-5D-5L: change from baseline in NT-proBNP, TnI, and EQ-5D-5L (to allow for analysis after the study). − Following approval of tafamidis in some regions, clarified the ability to use tafamidis after at least 24 months of double-blind treatment. − Clarified that participants may withdraw from the study at any time. − Immunoelectron microscopy added as a diagnostic method to Screening criteria in order to assist with confirmation of the diagnosis of ATTR-CM in patients with concurrent MGUS. − Clarified requirement for immunofixation of serum and urine. − The requirement of confirmation of diagnosis of ATTR-CM by central review of clinical data was deleted from the eligibility criteria but a clarification on the timeframe for confirmation of diagnosis by central review was added. − Clarified that the two 6MWTs did not need to be consecutive and that a third test (if needed) should be repeated within 24 hours to 1 week. − Transient ischemic attack was added as an exclusionary condition. − Revised threshold to allow for risk/benefit assessments at higher levels of NT-proBNP. − Changed blanket exclusionary concomitant medications of calcium channel blockers and digitalis to exclusion of calcium channel blockers for those with conduction system effects, to allow use of dihydropyridine calcium channel blockers, and to allow use of digoxin if required for management of atrial fibrillation with rapid ventricular response. − Removed the use of study drug dosing diaries. − Removed requirement to assess vital signs postdose. − Changed the per-protocol population to include all participants from the mITT set who did not have major protocol violations or deviations. − Secondary endpoint analyses changed to include Cox regression model adjusting for stratification factors. − Definition of CV-related hospitalization was clarified.
13 February 2020	− Increased number of study centers. − Immunohistochemistry was added as a diagnostic method to the Screening criteria in order to assist with confirmation of the diagnosis of ATTR-CM in patients with concurrent MGUS. − Deleted text on adjustment of study drug dose to 400 mg. − Clarified ability to use tafamidis after at least 12 months of double-blind treatment. The change from 24 months to 12 months was made to decrease the potential that participants may discontinue from the study in order to access tafamidis. This change was based on the feedback from the study Steering Committee and Principal Investigators in light of approval of tafamidis for ATTR-CM in some participating countries [eg, USA approval: May 2019; EU: February 2020 (Maurer et al., 2018; Vyndaqel-EPAR, 2019)].
14 January 2021	− Added guidance on some study procedures. − Added that EOCIs adjudicated by CEC as not CV-related were to be considered AEs. − Added that EOCIs were considered part of efficacy endpoint of CV-related hospitalizations.

31 March 2021	− Revised the F-S test of the primary endpoint to reflect the addition of change from baseline in 6MWD: a hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWD over a 30-month fixed treatment duration. − OLE was removed as separate OLE study. − Clarified elements of PK-PD substudy and added PopPK analysis and PK-PD relationship as exploratory endpoints. − Updated statistical plan for control of α. − Added guidance on some study procedures.
16 June 2022	− Revised the F-S test of the primary endpoint to reflect addition of NT-proBNP: a hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization, change from baseline in NT-proBNP, and change from baseline in 6MWD over a 30-month fixed treatment duration. − Promoted two secondary objectives/endpoints to key secondary objectives/endpoints: 1) change from baseline to Month 30 in serum TTR (prealbumin) level (an in vivo measure of TTR stabilization); 2) all-cause mortality by Month 30 including death due to any cause, heart transplant, or CMAD. − Revised secondary objectives and associated endpoints: 1) moved key primary endpoint "A hierarchical combination of all-cause mortality, cumulative frequency of CV-related hospitalization, and change from baseline in 6MWD over a 30-month fixed treatment duration" and the associated objective to the secondary endpoint/objective section; 2) promoted exploratory endpoint "Change in NT-proBNP from baseline to Month 30 of treatment" and associated objective to secondary objective/endpoint section. − Clarified discontinuation of participants from therapy or withdrawal from the study. − Clarified Investigator-responsibilities for collection and documentation of potential study endpoints, with particular reference to adjudicated events. − Added definition of CMAD. − Added text clarifying that an independent CEC was to review and adjudicate "heart transplant, CMAD" to determine whether they met the definition of protocol-specified efficacy endpoints. − Added guidance on some study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported