Clinical trial results:
AdreView™ Myocardial Imaging for Risk Evaluation – A Multicentre Trial to Guide ICD Implantation in NYHA class II & III Heart Failure Patients With 30%LVEF35% ADMIRE-ICD

Summary

EudraCT number	2015-001464-19
Trial protocol	HU ES NL CZ DE DK
Global end of trial date	04 May 2018

Results information

Result version number	v1 (current)
This version publication date	27 April 2019
First version publication date	27 April 2019

Trial information

Trial identification

Sponsor protocol code	GE-122-020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02656329
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GE Healthcare Ltd.
Sponsor organisation address	The Grove Centre, White Lion Road, Amersham, Buckinghamshire, United Kingdom, HP7 9LL
Public contact	Medical Director - Nuclear Medicine, GE Healthcare Ltd., info@ge.com
Scientific contact	Medical Director - Nuclear Medicine, GE Healthcare Ltd., info@ge.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	30 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation in a population of New York Heart Association (NYHA) class II and III Heart Failure (HF) subjects with 25%≤left ventricular ejection fraction (LVEF) ≤35%. This will be achieved by comparing allcause mortality observed in the AdreView™-guided therapy group to that observed in subjects receiving the Standard of Care (SoC; defined as the medical care as recommended by internationally accepted HF guidelines), in whom no clinical decision will be made based upon AdreView™ scan results.

Protection of trial subjects:

This study was conducted in full accordance with the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH), and any applicable national and local laws and regulations. The investigators were responsible for performing the study in accordance with the protocol and ICH E6-Good Clinical Practice (GCP), for collecting, recording, and reporting the data accurately and properly. The informed consent process was documented in the subject's medical record and the investigator signed, dated and timed the informed consent form after the subject had signed, dated and recorded the time. The study was designed and endorsed by a Steering/Scientific Committee composed of world leaders in heart failure (HF) and arrhythmia management.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 December 2015
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: 79
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	European Union: 248
Worldwide total number of subjects	343
EEA total number of subjects	0

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)	179
From 65 to 84 years	161
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The Study was conducted at 70 centers in United States of America, Canada and Europe between 30 December 2015 and 04 May 2018. A total of 395 subjects were enrolled in study, of which 52 were screen failures mainly due to exclusion criteria met.

Pre-assignment

Screening details:

Out of 343 subjects, 321 subjects with 25% <=left ventricular ejection fraction (LVEF) <=35% were randomized in a 1:1 ratio to the AdreView™ group or Standard of Care (SoC) group stratified by enrolling center via an interactive web response system and 22 subjects were not randomized but included in safety analysis set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AdreView™

Arm description:

Subjects received 1 intravenous injection of 10 millicuries (mCi) (370 MBq) of AdreView™ (Iobenguane I-123 Injection). Subjects with AdreView™ Heart-to-Mediastinal ratio (H/M) <1.6 underwent Implantable Cardioverter Defibrillator (ICD) device implantation and H/M >= 1.6 continued to receive Guideline-Directed Optimal Medical Therapy (GDMT) according to clinical standard practice.

Arm type	Experimental
Investigational medicinal product name	AdreView™
Investigational medicinal product code	
Other name	Iobenguane I123 Injection
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AdreView™ was administered in a volume of 5 mL (diluted using 0.9% sodium chloride as needed) and injected as a slow infusion over 1 to 2 minutes followed by 10 mL of saline flush injected over a maximum of 5 seconds.

Arm title	Standard of Care

Arm description:

Subjects received 1 intravenous injection of 10 mCi (370 MBq) of AdreView™ (Iobenguane I-123 Injection) and underwent ICD implantation and were followed up in accordance with internationally accepted Heart Failure (HF) guidelines.

Arm type	Experimental
Investigational medicinal product name	AdreView™
Investigational medicinal product code	
Other name	Iobenguane I123 Injection
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

AdreView™ was administered in a volume of 5 mL (diluted using 0.9% sodium chloride as needed) and injected as a slow infusion over 1 to 2 minutes followed by 10 mL of saline flush injected over a maximum of 5 seconds.

Number of subjects in period 1[1]	AdreView™	Standard of Care
Started	164	157
Completed	0	0
Not completed	164	157
Other than specified above	5	6
Consent withdrawn by subject	7	6
Study terminated by sponsor	150	142
Lost to follow-up	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 343 subjects were included in study. Of which, 321 subjects were randomized in a 1:1 ratio to the AdreView™ group or Standard of Care (SoC) group stratified by enrolling center via an interactive web response system and 22 subjects were not randomized but included in safety analysis set.

Baseline characteristics

Reporting groups	
Reporting group title	AdreView™
Reporting group description:	
Subjects received 1 intravenous injection of 10 millicuries (mCi) (370 MBq) of AdreView™ (Iobenguane I-123 Injection). Subjects with AdreView™ Heart-to-Mediastinal ratio (H/M) <1.6 underwent Implantable Cardioverter Defibrillator (ICD) device implantation and H/M >= 1.6 continued to receive Guideline-Directed Optimal Medical Therapy (GDMT) according to clinical standard practice.	
Reporting group title	Standard of Care
Reporting group description:	
Subjects received 1 intravenous injection of 10 mCi (370 MBq) of AdreView™ (Iobenguane I-123 Injection) and underwent ICD implantation and were followed up in accordance with internationally accepted Heart Failure (HF) guidelines.	

Reporting group values	AdreView™	Standard of Care	Total
Number of subjects	164	157	321
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.1	62.1	
standard deviation	± 9.40	± 10.05	-
Gender categorical Units: Subjects			
Female	35	22	57
Male	129	135	264
Ethnicity Units: Subjects			
Hispanic or Latino	17	9	26
Not Hispanic or Latino	142	140	282
Unknown or Not Reported	5	8	13
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	9	19
White	149	137	286
More than one race	0	0	0
Unknown or Not Reported	5	8	13

End points

End points reporting groups

Reporting group title	AdreView™

Reporting group description:

Subjects received 1 intravenous injection of 10 millicuries (mCi) (370 MBq) of AdreView™ (Iobenguane I-123 Injection). Subjects with AdreView™ Heart-to-Mediastinal ratio (H/M) <1.6 underwent Implantable Cardioverter Defibrillator (ICD) device implantation and H/M >= 1.6 continued to receive Guideline-Directed Optimal Medical Therapy (GDMT) according to clinical standard practice.

Reporting group title	Standard of Care

Reporting group description:

Subjects received 1 intravenous injection of 10 mCi (370 MBq) of AdreView™ (Iobenguane I-123 Injection) and underwent ICD implantation and were followed up in accordance with internationally accepted Heart Failure (HF) guidelines.

Primary: All-cause Mortality

End point title	All-cause Mortality

End point description:

All-cause mortality included deaths of subjects due to any cause. Percentage of subjects who died due to any cause were reported. Analysis was performed on full analysis set (FAS) that was defined as subjects included in the safety analysis set who were randomised to the AdreView™ group or the SoC group.

End point type	Primary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	3.0	3.2		

Statistical analyses

Statistical analysis title	AdreView™ vs. Standard of Care

Statistical analysis description:

Analysis was performed using the Cox proportional hazards model stratified by enrolling center, with method of treatment guidance (SoC vs AdreView™ group) as the only covariate.

Comparison groups	AdreView™ v Standard of Care

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.8459 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.295
upper limit	3.719

Notes:

[1] - Non-inferiority of AdreView™ group over SoC group was demonstrated if upper bound of the 95% confidence interval (CI) for the hazard ratio (HR) (AdreView™ group / SoC) was equal to 1.20.
[2] - Threshold for significance at 0.025 level.

Secondary: Percentage of Subjects With Events of Complications of Device: H/M >=1.6 in Full Analysis Set

End point title	Percentage of Subjects With Events of Complications of Device: H/M >=1.6 in Full Analysis Set

End point description:

Composite of the percentage of subjects with events of hospitalization or death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery), complications of long-term device therapy (i.e., infection not leading to hospitalization, lead and/or generator removal/replacement, inappropriate shocks, explanation), and combined as 'complications of device' for subjects with H/M >=1.6. Subjects who were alive at time of database lock (DBL) were censored at the last known-alive date. Analysis was performed on FAS population. Here, number of subjects analysed = subjects with H/M >=1.6.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	20		
Units: percentage of subjects				
number (not applicable)				
Hospitalisation/death	3.8	0		
Complications of long-term device therapy	3.8	15.0		
Complications of device	3.8	15.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cardiac Death

End point title	Percentage of Subjects With Cardiac Death

End point description:

Cardiac death composed of sudden cardiac death, death due to cardiac arrhythmia, death due to heart failure, and death due to other cardiovascular causes. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	1.2	0.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hospitalization for Cardiovascular Cause

End point title	Percentage of Subjects With Hospitalization for Cardiovascular Cause

End point description:

Percentage of subjects who were hospitalised for cardiovascular cause were reported. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	7.3	7.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With All-Cause Hospitalization

End point title	Percentage of Subjects With All-Cause Hospitalization

End point description:

Percentage of subjects with all-cause hospitalization were reported. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	17.1	22.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Events (Composite of the Occurrence of Resuscitated Life-Threatening Ventricular Tachycardia, Unstable Ventricular Tachyarrhythmias, Sudden Cardiac Death [SCD] and Resuscitated Cardiac Arrest)

End point title	Percentage of Subjects With Events (Composite of the Occurrence of Resuscitated Life-Threatening Ventricular Tachycardia, Unstable Ventricular Tachyarrhythmias, Sudden Cardiac Death [SCD] and Resuscitated Cardiac Arrest)

End point description:

Percentage of subjects with composite events i.e. occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachy-arrhythmias, SCD and resuscitated cardiac arrest were reported. Subjects who were alive at time of database lock (DBL) were censored at the last known-alive date. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	1.2	2.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Syncope

End point title	Percentage of Subjects With Syncope

End point description:

Percentage of subjects with Syncope were reported. Subjects who were alive at time of DBL were censored at the last known-alive date by date of DBL. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	2.4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Implantable Cardioverter Defibrillator (ICD) Implantation

End point title	Percentage of Subjects With Implantable Cardioverter Defibrillator (ICD) Implantation

End point description:

Percentage of subjects with ICD implantation were reported. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)	73.2	81.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Events of Complications of Device

End point title	Percentage of Subjects With Events of Complications of Device

End point description:

Composite of the percentage of subjects with events of hospitalization or death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery), complications of long-term device therapy (i.e., infection not leading to hospitalization, lead and/or generator removal/replacement, inappropriate shocks, explanation), and combined as 'complications of device'. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From randomization until the end of the follow-up period (median 304 days)

End point values	AdreView™	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	157		
Units: percentage of subjects				
number (not applicable)				
Hospitalization/death	4.9	3.8		
Complications of long-term device therapy	4.3	6.4		
Complications of device	5.5	6.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from randomization until the end of the follow-up period (median 304 days) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are study-emergent AEs that is AEs and deaths that developed/worsened during any time after randomization. Analysis was performed on safety population which included all subjects who signed the informed consent form and met all the inclusion criteria and none of the exclusion criteria.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	AdreView™

Reporting group description:

Subjects received 1 intravenous injection of 10 mCi (370 MBq) of AdreView™ (Iobenguane I-123 Injection). Subjects with AdreView™ H/M ratio <1.6 underwent ICD device implantation and H/M ratio >= 1.6 continued to receive GDMT according to clinical standard practice.

Reporting group title	Standard of Care

Reporting group description:

Subjects received 1 intravenous injection of 10 mCi (370 MBq) of AdreView™ (Iobenguane I-123 Injection) and underwent ICD implantation and were followed up in accordance with internationally accepted HF guidelines.

Reporting group title	Total Subjects

Reporting group description:

All subjects who were randomized in AdreView™ and Standard of Care group in addition with non-randomized subjects who signed informed consent form.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported in this study.

Serious adverse events	AdreView™	Standard of Care	Total Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 164 (39.63%)	62 / 157 (39.49%)	127 / 343 (37.03%)
number of deaths (all causes)	6	5	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Gastrointestinal stromal cancer			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm prostate			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 164 (1.22%)	1 / 157 (0.64%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Implantable defibrillator insertion			

subjects affected / exposed	2 / 164 (1.22%)	1 / 157 (0.64%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site irritation			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyp			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 164 (1.22%)	1 / 157 (0.64%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sinus congestion			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device inappropriate shock delivery			
subjects affected / exposed	3 / 164 (1.83%)	2 / 157 (1.27%)	5 / 343 (1.46%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device use issue			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lead dislodgement			
subjects affected / exposed	2 / 164 (1.22%)	2 / 157 (1.27%)	4 / 343 (1.17%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood uric acid increased			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sternal fracture			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 164 (0.61%)	2 / 157 (1.27%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina unstable			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	5 / 164 (3.05%)	2 / 157 (1.27%)	7 / 343 (2.04%)
occurrences causally related to treatment / all	0 / 11	0 / 2	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 164 (1.83%)	3 / 157 (1.91%)	7 / 343 (2.04%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	3 / 164 (1.83%)	1 / 157 (0.64%)	4 / 343 (1.17%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	26 / 164 (15.85%)	22 / 157 (14.01%)	48 / 343 (13.99%)
occurrences causally related to treatment / all	0 / 38	0 / 28	0 / 68
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 6
Cardiac failure			
subjects affected / exposed	8 / 164 (4.88%)	5 / 157 (3.18%)	13 / 343 (3.79%)
occurrences causally related to treatment / all	0 / 9	0 / 8	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 164 (0.61%)	2 / 157 (1.27%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac perforation			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 164 (0.61%)	4 / 157 (2.55%)	5 / 343 (1.46%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer’s type			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	4 / 164 (2.44%)	1 / 157 (0.64%)	5 / 343 (1.46%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal ulcer			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 164 (1.22%)	1 / 157 (0.64%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren’s contracture			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 164 (1.83%)	0 / 157 (0.00%)	3 / 343 (0.87%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 164 (1.22%)	3 / 157 (1.91%)	5 / 343 (1.46%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 164 (2.44%)	1 / 157 (0.64%)	5 / 343 (1.46%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Post procedural cellulitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 164 (0.00%)	2 / 157 (1.27%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	2 / 164 (1.22%)	0 / 157 (0.00%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyslipidaemia			

subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 157 (0.64%)	2 / 343 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 157 (0.00%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin D deficiency			

subjects affected / exposed	0 / 164 (0.00%)	1 / 157 (0.64%)	1 / 343 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AdreView™	Standard of Care	Total Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 164 (0.00%)	0 / 157 (0.00%)	0 / 343 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2016	Following amendments were made: - Inclusion criterion was revised to allow LVEF assessment performed within 3 months before or at the time of enrollment to be used. This change increased the flexibility of investigators to recruit subjects without having an impact on subject safety, scientific validity of the trial, or quality of the data. The amended criterion continued to adhere to international HF guidelines and additional wording stipulating a 40-day time lapse between hospitalization for HF or acute coronary syndrome ensured that inclusion criterion remained applicable in case the LVEF determination was made before the time of enrollment. - A blood sample for NT-proBNP was added as an alternative to BNP.
11 May 2017	The LVEF window was revised from 30%≤LVEF≤35% to 25%≤LVEF≤35%. As part of their remit, the Executive Steering Committee (ESC) continuously evaluated scientific data to ensure that trial integrity was aligned with up to date scientific evidence. Recent scientific evidence indicated that the benefits of additional risk stratification in subjects with HF and reduced ejection fraction with LVEF of 30 to 35% may be also applicable to subjects with lower LVEF values. Therefore, modification of the LVEF window from 30%≤LVEF≤35% to 25%≤LVEF≤35% was recommended by the ESC. The DSMB endorsed this change. The ESC discussed this amendment with the Data Safety Monitoring Board (DSMB) who noted that extending the study recruitment to LVEF values of 25 to 30% would still recruit subjects for whom good stratification was possible. The introduction and rationale were updated to support this. - The sample size was recalculated based on modification of the LVEF entry criteria. Minor clarifications to the primary and secondary efficacy analysis were included. - Investigators were reminded that subjects with HF were considered potential candidates for ICD implantation for primary prevention of SCD only after they had been under GDMT for at least 3 months. - Investigators were reminded that should any subjects not be receiving GDMT at target dose per local guidelines, the investigator must document the reason(s) why in the source documents. - The option to use an administration volume of up to 15 mL AdreView™ (to be achieved by combining the contents of up to 3 unit dose vials of IMP as necessary to obtain the correct amount of activity) was included to accommodate use in sites where there were logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 March 2018	The study was early terminated by sponsor after enrollment of 395 participants due to very slow recruitment rates. Sample size was 395 participants instead of planned 2354 participants.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to termination of the study by the Sponsor, the sample size was not sufficient for the hierarchical hypothesis testing.

Notes: