Clinical Study Protocol **GE Healthcare**
GE-122-020

Title: AdreView™ Myocardial Imaging for Risk Evaluation – A multicentre trial to guide ICD implantation in NYHA class II & III heart failure patients with 25%≤LVEF≤35%. ADMIRE-ICD

REVISED TO INCORPORATE AMENDMENT A02

Sponsor

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "Sponsor")

EudraCT Number: 2015-001464-19

Medical Director

Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature

Date

Print Name

1 SYNOPSIS

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Title of Study: AdreView™ Myocardial Imaging for Risk Evaluation – A multicentre trial to guide ICD implantation in NYHA class II & III heart failure patients with 25%≤LVEF≤35%. ADMIRE-ICD

Protocol Number: GE-122-020

Investigators and Study Centres: Approximately 130 centres located in the United States of America, Canada and Europe.

Phase of Development: Phase IIIb (indication for guiding implantable cardioverter defibrillator [ICD] implantation)

Objectives:

Primary Objective:

- 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) patients with 25%≤left ventricular ejection fraction (LVEF) ≤35%. This will be achieved by comparing all-cause mortality observed in the AdreView™-guided therapy group to that observed in patients 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.

Secondary Objectives:

- Compare the rate of hospitalisation and death related to major complications of ICD implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation) in patients randomised to the AdreView group with a heart-to-mediastinal ratio (H/M) ≥1.6 with patients in the SoC group with an H/M ≥1.6.
- Compare AdreView™-guided therapy to SoC therapy for:
  - The occurrence of cardiac death (composed of sudden cardiac death (SCD), death due to cardiac arrhythmia, death due to HF, and death due to other cardiovascular causes).
  - The rate of hospitalisation for cardiovascular cause.
  - The rate of all-cause hospitalisation.
  - A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachy-arrhythmias, SCD and resuscitated cardiac arrest
  - The occurrence of syncope.
  - The clinical and healthcare resource utilisation data including, ICD implantation, all hospitalisations, treatment of adverse events (AEs), and AdreView™ administration.
- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). (AdreView™ group vs SoC).

Exploratory Objectives:

- [redacted]

Study Design:

This is an event-driven Phase IIIb, multicentre, randomised, clinical study to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation, in NYHA class II and III HF

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patients with 25%≤LVEF≤35%, and in particular, for identifying patients who are at low risk for SCD and who would not benefit, or may suffer harm, from implantation of an ICD device.

The study has been designed and endorsed by a Steering/Scientific Committee composed of world leaders in HF and arrhythmia management. Three committees will be formed in order to ensure proper scientific and ethical conduct of the study:

- An Executive Steering Committee (ESC) will oversee the conduct of the study and will make recommendations to the Sponsor based on the outputs of the other 2 committees.
- A Critical Events Adjudication Committee (CEAC) will adjudicate the study endpoints.
- A Data Safety Monitoring Board (DSMB) will oversee the overall study safety.

The endpoints in this study will be directly related to the health outcomes in both randomised groups. They will be standardised and assessed by an independent CEAC in a blinded fashion in order to capture all those major events that are directly related to the efficacy of the strategies tested. The CEAC will set up their rules prospectively so that an objective adjudication can take place with the intent of capturing all those outcomes that are relevant in these patients. No members of the CEAC will be allowed to participate as site investigators, recruiting physicians or be directly involved in the care of study patients.

The DSMB will act as an independent committee overseeing all safety aspects of the study, and is comprised of experts with relevant experience in, cardiology, clinical trials safety, biostatistics and epidemiology. The DSMB members are independent of investigators entering or caring for patients in the study, are independent of the other study committees and are not involved in any other of the study activities than their role in the DSMB. The DSMB may recommend to the ESC and Sponsor termination of the study at any time should prospective ethical or safety guidelines not be met, or propose protocol amendments to ensure safety of study individuals. In addition, based on the regular or interim analyses performed, the DSMB may recommend to the ESC and Sponsor to re-calculate the sample size, or prolong or terminate the study should the power of the study become non-sufficient to achieve its objectives.

This study will be conducted at approximately 130 centres in the USA, Canada and Europe. At least 2354 patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least 2001 patients in the study.

It is anticipated that patients will participate in the study until sufficient endpoints have been accrued which may correspond to an average of 2.75 to 3 years individual follow-up. The total study duration is expected to be approximately 6 years and the total required number of primary endpoint events observed is 247.

Only patients with stable heart failure who have been under guideline-directed optimal medical therapy for at least 3 months and have 25%≤LVEF≤35% will be considered for inclusion. Patients must have 25%≤LVEF≤35% as measured in the previous 3 months before enrolment with no hospitalisations for HF or acute coronary syndrome during this period of time. In case these patients have a hospitalisation for HF or acute coronary syndrome, the LVEF measurement will only be valid if performed 40 days after this event. Patients without a LVEF measurement will have the test performed at screening.

Patients with 25%≤LVEF≤35%, and meeting all other inclusion criteria and not meeting any of the exclusion criteria, will be enrolled and randomly assigned to the AdreView™ group or the SoC group. All patients will be scheduled for an AdreView™ scan. The results of the AdreView™ scan in the SoC group will remain blinded to the investigator to avoid any influence in the decision of implanting an ICD. The results of the AdreView™ scan in the AdreView™ group will be known to the investigator and as such be used to assess their cardiovascular risk level and determine ICD implantation. Patients with AdreView™ H/M ratio <1.6 (high 1- and 2-year mortality risk) will undergo ICD device implantation. Patients with AdreView™ H/M ratio ≥1.6 (low 1- and 2-year mortality risk) will continue to receive guideline-directed optimal medical therapy according to clinical standard practice and will not undergo ICD implantation. Patients in this later group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. Patients allocated

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to the SoC group will undergo ICD implantation and will be managed and followed up in accordance with internationally accepted HF guidelines.
Patients will attend follow-up visits at the rate determined by the investigator, in accordance with their clinical standard practice. However, a follow-up visit must take place at least every 6 months (an extra follow-up visit will be performed at 3 months after ICD implantation). All patients will also attend an end-of-study visit.

Selection of Patients:

Inclusion Criteria:

Patients may be included in the study if they meet all of the following criteria:

(1) Patients ≥18 years of age at the time dated informed consent is obtained.
(2) Female patients must be pre-menarchal, surgically sterile (had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for more than 1 year), non-lactating, or, if of childbearing potential, a serum or urine pregnancy test with the results known prior to AdreView™ (Iobenguane I^{123} Injection) administration) is negative.
(3) Patients willing and able to comply with all study procedures and a signed and dated informed consent is obtained before any study-procedure is carried out.
(4) Heart failure NYHA class II or III for symptoms, patients with ischemic or non-ischemic heart disease, eligible for ICD implantation as per each site's standard of practice.
(5) Non-ischemic dilated cardiomyopathy or ischemic heart disease of at least 3 months duration receiving guideline-directed optimal medical therapy.
(6) 25%≤LVEF≤35%, performed within 3 months before or at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted].
In case LVEF measurement is performed within 3 months before enrolment, measurement should be performed at least 40 days after a hospitalisation for HF or acute coronary syndrome (including myocardial infarction), and to be valid, method of measurement should be in accordance with the protocol and the imaging exam should be made available to the Sponsor in digital format.
In case several valid LVEF measurements are available, the closest to enrolment will be used for inclusion determination.
(7) Clinically stable HF in the medical judgment of the investigator (i.e., no significant changes in medication, no worsening of symptoms, no unscheduled visits to the doctor's office) for the past 30 days and no hospitalisation for HF or acute coronary syndrome (including myocardial infarction) in the past 40 days.
(8) Reasonable expectation of meaningful survival for at least 1 year.

Exclusion Criteria:

Patients must be excluded from participating in this study if they meet any of the following criteria:

(1) Patients with existing ICD or patient having an indication of ICD implantation for secondary prevention of SCD.
(2) Hospitalisation for HF or for acute coronary syndrome in the previous 40 days.
(3) Patients where a cardiac resynchronisation therapy (CRT) is planned or indicated
(4) Other indication for placement of device (sustained ventricular tachycardia, resuscitated sudden death, need for atrioventricular pacing).
(5) NYHA class I or class IV symptoms at the time of study entry.
(6) American College of Cardiology-American Heart Association (ACC-AHA) class III or class IV (unstable) angina.
(7) Patient with chronic renal insufficiency defined as serum creatinine ≥3 mg/dl (or ≥265.2 µmol/L).
(8) Known or suspected hypersensitivity/allergy to Iobenguane or to any of the excipients in AdreView™

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(Iobenguane I^{123} Injection).

(9) Patient who is pregnant or plans to become pregnant within 2 weeks after AdreView™ (Iobenguane I^{123} Injection) administration.

(10) Patient who has used any medication in the 2 weeks before AdreView™ (Iobenguane I^{123} Injection) that could interfere with the test: e.g., but not limited to amitriptyline or derivatives, imipramine or derivatives, other antidepressants or drugs known or suspected to inhibit the norepinephrine transporter, antihypertensives that deplete norepinephrine stores or inhibit reuptake, sympathomimetic amines or cocaine.

(11) Patients that have a medical condition that could interfere with the AdreView™ test (e.g., but not limited to left ventricular assist device, or prior heart transplant).

(12) Patients who participated in a clinical study involving a drug or device within 30 days prior to study entry and patients participating in any other clinical study.

(13) Patients having serious non-cardiac medical condition associated with significant elevation of plasma catecholamines, including pheochromocytoma.

(14) Patients with a clinical diagnosis of (or being treated for) Parkinson's disease or Multiple System Atrophy.

(15) The patient has participated in a research study using ionizing radiation in the previous 12 months.

(16) Patients previously randomized in this study.

Number of Patients/Centres Planned:

At least 2354 patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least 2001 patients in the study at approximately 130 centres.

Treatment of Patients:

Investigational Medicinal Product (IMP):

After randomisation to either the AdreView™ group or the SoC group, all patients will receive an intravenous injection of 10 mCi (370 MBq) of AdreView™. A ±10% tolerance of the nominal dose will be allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) in accordance with the Package Insert/Summary of Product Characteristics/Investigator's Brochure (IB). AdreView™ will be 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. Patients being allocated to the AdreView™ low-risk group will receive a second injection of AdreView™ and planar/SPECT imaging 2 years after the first one. If any of these patients voluntarily withdraw prior to completion of the study they will be offered this second AdreView™ scan prior to withdrawal being effective.

Comparator:

No comparator imaging modality(ies) will be used. The main comparator will be medical SoC (defined as the medical care as recommended by internationally accepted HF guidelines).

Duration of Study:

This will be an event-driven study. Patients will be enrolled and followed up until 247 primary endpoint events have occurred in the study. The expected duration of the study is approximately 6 years (assuming a 32-month recruitment period and a mean observational time per patient of 2.75 to 3 years). A recommendation from the DSMB may lead to an early termination of the study as defined in the DSMB charter.

Efficacy and Safety Variables

Primary Endpoint:

- The primary endpoint will be all-cause mortality.

Secondary Endpoints:

Key Secondary Endpoints:

- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator

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removal/replacement, inappropriate shocks, explantation). (AdreView™ Low-risk group vs SoC H/M ≥1.6)

- Cardiac death (composed of SCD, death due to cardiac arrhythmia, death due to HF, and death due to other cardiovascular causes).
- The rate of hospitalisation for cardiovascular cause.
- The rate of all-cause hospitalisation.
- A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachyarrhythmias, SCD and resuscitated cardiac arrest.

Additional Secondary Endpoints:

- The occurrence of syncope.
- The clinical and healthcare resource utilisation data including, ICD implantation, all hospitalisations, treatment of AEs, and AdreView™ administration.
- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation) (AdreView™ group vs SoC).

The above listed primary and secondary endpoints (except those only economic) will be reviewed and validated by the CEAC for all patients.

Exploratory Endpoint:

- [redacted]

Safety Endpoints:

Safety variables will be the same as the efficacy variables plus AEs related to the administration of the product, and ICD therapies.

Statistical Methods and Planned Analysis:

Primary Analyses:

The primary endpoint is all-cause mortality.

This is an event-driven study. The primary efficacy analysis will take place after 247 instances of the primary efficacy endpoint have accrued. The primary efficacy endpoint will be analysed for non-inferiority. If the upper bound of the confidence interval is less than 1.0, superiority will be claimed/established.

The primary null hypothesis is: H_0: hazard ratio (HR) (AdreView™ group / SoC) $\geq HR_0$.

The primary alternative hypothesis is: H_a: HR (AdreView™ group / SoC) $< HR_0$.

For this study, HR_0 is chosen to be 1.20.

The primary efficacy analysis will be performed in the primary efficacy population using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (SoC vs AdreView™ group) as the only covariate.

This analysis will be performed at a 1-sided alpha value of 0.025.

Supportive Analyses:

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (AdreView™ group vs. SOC), LVEF, NYHA Classification, and b-type natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP), as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

Secondary Analyses:

If the primary efficacy analysis is statistically significant, the key secondary endpoints will be analysed in hierarchical order. If the analysis of the first key secondary endpoint is statistically significant, then the hierarchical analysis will continue with analysis of the second key secondary endpoint. However, if the analysis of

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the first key secondary endpoint is not statistically significant, then the hierarchical analysis will stop after analysis of the first key secondary endpoint. This method will continue until either all of the key secondary endpoints have been analysed hierarchically or the analysis of one of the key secondary endpoints is not statistically significant, at which point the hierarchical analysis of key secondary endpoints will stop.
The non-key secondary endpoints will be analysed inferentially, but not hierarchically.

Key Secondary Endpoints:

- A composite of the proportion of patients with hospitalisation or death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) or complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). This endpoint will be analysed for superiority. These proportions will be compared between the patients with H/M ≥1.60 in the AdreView™ group and the patients with H/M ≥1.60 in the SoC group, using the Cochran-Mantel-Haenszel test stratified by enrolling centre, using a 2-sided alpha value of 0.050.
- Cardiac death. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority [NI], using an NI margin of 1.20).
- Rate of hospitalisation for cardiovascular cause. This rate will be compared between the AdreView™ and SoC groups using the Miettinen and Nurminen methodology [Miettinen and Nurminen 1985], (non-inferiority [NI], using an NI margin of 1.20).
- Rate of all-cause hospitalisation. This rate will be compared between the AdreView™ and SoC groups using the Miettinen and Nurminen methodology [Miettinen and Nurminen 1985], (NI, using an NI margin of 1.20).
- A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachy-arrhythmias, SCD and resuscitated cardiac arrest. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority, using an NI margin of 1.20).

Additional Secondary Endpoints:

- Syncope. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority, using an NI margin of 1.20).
- Clinical and healthcare resource utilisation data collected in this study including ICD implantation, all hospitalisations, treatment of AEs, and AdreView™ administration will be used in an economic evaluation of study outcomes for relevant geographies. These clinical and healthcare resource utilisation data will be summarised in the primary efficacy population and compared between the AdreView™ and SoC groups. These data will be analyzed with a superiority analysis, using a 2-sided alpha value of 0.05. These data may also be used for future health economic analyses.
- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation) (AdreView™ group vs SoC). The occurrence of these events will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis. These data will be analyzed with a superiority analysis, using a 2-sided alpha value of 0.05.

Exploratory Efficacy Analyses:

[redacted].

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[redacted]

Safety Analyses:
The safety variables to be analysed include all events occurring after informed consent, all adverse events (AEs), including AdreView™-emergent AEs, serious adverse events (SAEs), vital sign data, physical examination results, clinical laboratory test data, and electrocardiographic data. All safety analyses will be performed in the safety population.
All events occurring after informed consent and AEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. An overall summary of AEs will be presented. AdreView™-emergent AEs will also be presented by causal relationship to study drug. Summaries of SAEs, AdreView™-emergent SAEs and other significant AEs will also be presented.
For vital signs, clinical laboratory tests, ECG data, and baseline values will be summarised with descriptive statistics (mean, standard deviation, median, minimum, and maximum) for each enrolment group. For vital signs, post-enrolment changes from baseline and shift tables of all post-administration changes from baseline versus time will also be generated for each cohort. In addition, potentially clinically significant values will be summarised for vital sign parameters. Physical examination data will be presented by enrolment group and time point. All safety data will be listed by enrolment group and patient number.

Sample size estimation (assumptions):
The all-cause mortality rate that is expected in the study has been estimated using the all-cause mortality rate observed in Study GE-122-016 at 36 months (internal report). It is assumed:

	Patients with 25%≤LVEF≤30%		**Patients with 30%≤LVEF≤35%**	
	%	**Mortality Rate**	**%**	**Mortality Rate**
H/M ratio <1.6	79%	20.25%	75%	15.14%
H/M ratio ≥1.6	21%	9.72%	25%	4.68%

In addition, the following observations or assumptions were taken: the ratio of patients with 25%≤LVEF≤30% vs 30%≤LVEF≤35% is expected to be 1:4 to account for the prior enrollment of only patients with 30%≤LVEF≤35%; the hazard ratio of patients with ICD implantation vs with usual care in the existing practice is 0.9 [Køber et al. 2016]. Referring to existing practice, only 15% of patients with 25%≤LVEF≤35% currently receive ICD. Accordingly, the number of patients currently do not receive ICD but who will receive it according to protocol and the number of patients who currently receive ICD and who will not receive it according to protocol have been calculated. In addition, the all-cause mortality rate of patients currently not receiving ICD but who will receive according to protocol (85% of patients with H/M ratio<1.6 in the AdreView™ group) has been corrected to take into account the 31% reduction in all-cause mortality observed at 20 months in the Multicentre Automatic Defibrillator Implant Trial II (MADIT II) [Moss et al. 2012]. These assumptions led to a composite overall mortality rate of 11.34% in the AdreView™ group and 13.33% in the SoC group. The sample size is estimated with the hypothesis of not having a relative increase of mortality rate in excess of 20% and with the following assumptions:

- Alpha = 0.025, 1-sided.
- Statistical power = 80%.
- 1:1 randomisation to AdreView™ and SoC groups.
- H_0: $HR \geq HR_0$ vs H_1: $HR < HR_0$. $HR_0 = 1.20$.
- Assumed HR: 0.84

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- Accrual time: 18 months.
- Total study duration: 48 months.
- AdreView™ group survival rate at 36 months: 0.887.

Based on the above assumptions, the required total number of events will be 247, and the required total number of randomized patients will be 2001.

The planned study accrual will be at least 2354 patients screened in order to randomize at least 2001 patients in the study.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACC-AHA	American College of Cardiology-American Heart Association
ADMIRE	AdreView™ Myocardial Imaging for Risk Evaluation
AdreView™-emergent AE	Any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CEAC	Critical Events Adjudication Committee
CRO	Contract Research Organisation
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESC	Executive Steering Committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
H/M	Heart/Mediastinum
HR	Hazard Ratio
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional/Independent Review Board
IWRS	Interactive Web Response System
LVEF	Left Ventricular Ejection Fraction
MADIT	Multicentre Automatic Defibrillator Implant Trial
MedDRA	Medical Dictionary for Regulatory Activities
mIBG	Meta-iodobenzylguanidine
MPI	Myocardial Perfusion Imaging
MR	Magnetic Resonance Imaging
NI	Non-inferiority
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PT	Preferred Term
RCT	Randomised Clinical Trial
ROI	Regions of Interest
SAE	Serious Adverse Event

SCD	Sudden Cardiac Death
SD	Standard Deviation
SoC	Standard of Care
SOPs	Standard Operating Procedures
SPECT	Single Photon Emission Computed Tomography
USA	United States of America
WBC	White Blood Count

4 BACKGROUND INFORMATION AND STUDY RATIONALE

Approximately 5.1 million people in the United States of America (USA) have clinical manifestation of heart failure (HF) and the prevalence continues to increase [Yancy et al. 2013]. Similarly, the European Society of Cardiology estimates that 15 million Europeans suffer from HF with this number expected to rise to 30 million by 2020. Chronic HF is associated with high morbidity and mortality; the absolute mortality rate for HF remains at approximately 50% within 5 years of diagnosis.

In addition to medical therapies, device therapies are available and have proven effectiveness, especially for improving HF symptoms and preventing sudden cardiac death (SCD). However, optimizing risk stratification and appropriately triaging individual patients to these invasive options to improve clinical outcomes remains a clinical challenge [Yancy et al. 2013] [Goldberger et al. 2011].

Present USA and European Union (EU) guidelines recommend implantation of an implantable cardioverter defibrillator device (ICD) in patients with left ventricular ejection fraction (LVEF) ≤35% to reduce the risk of sudden death. Canadian guidelines [Bennett et al. 2017] further specify that additional risk assessment be performed in patients with LVEF values of 30% to 35% due to a lack of data supporting the use of prophylactic ICDs in this population. Moreover, the recently-reported DANISH study has questioned the utility of prophylactic ICD therapy in patients with non-ischemic left ventricular dysfunction, possibly due to the lower risk of arrhythmic death with contemporary medical therapy. Further, only about half of all patients who meet the guideline-derived criteria actually have an ICD implanted reflecting the uncertainly of ICD benefit in patients with lesser degrees of left ventricular dysfunction. For example, in the first year after ICD implantation, as few as 5% of patients will actually experience a potentially fatal arrhythmia for which an ICD therapy is necessary [Moss et al. 2012]. Thus, the majority of patients who have an ICD implanted do not receive a survival benefit from it. These patients are not immune from the complications of device implantation and on-going care, including mechanical and infectious complications of the procedure, inappropriate device activation, device failure, and ultimately need for device replacement. Despite optimal therapy and device care, approximately 2% of patients with devices will die suddenly each year, and 3% will die from other cardiac causes, usually HF or myocardial infarction. Moreover, inappropriate shocks are associated with a higher incidence of all cause and cardiovascular death [Moss et al. 2012]. Ideally, only patients who will suffer a serious arrhythmia would have an ICD implanted. Yet, it is unlikely that this degree of risk stratification is attainable, given temporal changes in their underlying heart disease.

Presently, the criterion widely used and accepted as a risk stratification tool for implantation of an ICD is a reduced LVEF, e.g., below 30% or 35% depending on local guidelines. This is based on multiple large-scale studies having demonstrated a benefit in terms of patient's survival. However, several publications have demonstrated that within the patients with an impaired LVEF, a low-risk group (and even a high-risk group) can be identified who may not benefit from an ICD implantation [Goldenberg et al. 2008] [Buxton et al. 2007]. For instance, in a post-hoc analysis of the Multicentre Automatic Defibrillator Implant Trial II (MADIT II) study, this low-risk group (having none of the clinical risk factors as defined by the Authors),

that represented nearly one third of the population included, had a 2-year mortality of 8% and not any benefit of ICD implantation was identified. Moreover, in the very high-risk group, no benefit was identified either [Goldenberg et al. 2008]. In the same study (MADIT II) it was also noted that only 35% of patients received appropriate shocks during a 3-year follow up [Chen and Zhou 2013].

More recently, the defined LVEF limits used in the MADIT I & II, DEFINITE, MUSTT and SCD-HeFT studies (upper LVEF limit ≤30 or ≤35%) have been questioned. [Al-Khatib et al. 2014] have suggested that perhaps devices for primary prevention of SCD should only be implanted in patients with LVEF <30%, identifying a population of patients with LVEF between 30% and 35% that might not benefit of ICD implantation, which implies that LVEF alone is not sufficient to select those who would benefit from this therapy. More recent scientific evidence suggests that there are groups of patients that can benefit from additional risk stratification beyond an LVEF cut-off point. Results of a multicentre, randomised trial in 1112 patients with non-ischemic heart failure (median LVEF 25%; mean follow up of 67.2 months) showed that prophylactic ICD implantation was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care [Køber et al. 2016]. A pooled analysis of 6 randomised controlled trials (RCTs) encompassing 2970 patients with non-ischemic HF (upper LVEF limit ≤30 or ≤35%) concluded that while there is a role for ICDs in this population, "improvement in risk prediction models can help overcome the traditional reliance on ejection fraction for risk stratification of sudden cardiac death in these patients" [Golwala et al. 2016]. Another pooled analysis of the results of SCD-HeFT, MADIT-II and DEFINITE (all with LVEF ≤35%), assessing the benefit of the ICD, in comparison with optimal medical therapy alone in NHYA class III patients (n=1054) showed no significant survival benefit [Barra et al. 2016]. Risk stratification could also be improved in class II HF patients. Per the revised ESC guidelines, an ICD will prevent about 2 deaths per year for every 100 devices in patients with mild HF (NYHA class II) [Ponikowski et al. 2016].

Therefore, using any LVEF cut-off point alone to identify patients at high risk of death and guide ICD implantation lacks the necessary accuracy. Additional biomarker tests may provide the necessary information to identify those patients who will benefit from an ICD.

Finally, ICD implant and care is expensive. In 2006, costs per implant per patient in the USA were estimated at USA$ 28,500-55,200 and annual follow up from USA$ 4,800-17,000 [Groeneveld et al. 2006]. A more recent study in the Netherlands found a life time costs for an ICD to range from € 60,800 to € 64,200 [Thijssen et al. 2014].

New tools are required to improve risk-stratification. Meta-iodobenzylguanidine (mIBG) is an analogue of norepinephrine that is taken up into cardiac sympathetic nerve endings in the same manner as NE. In HF this uptake is decreased and norepinephrine stores in the myocardium are depleted. This process can be imaged in situ by using scintigraphy with ^{123}I-mIBG which strongly correlates with established markers of HF severity. Findings on mIBG imaging are associated with poor outcomes, including risk of death or of requiring transplantation, and sudden death. In a study that included 81 HF patients with LVEF <35%, assessed by cardiac mIBG imaging at enrolment and followed-up for at least 5 years, [Kawai et al. 2015] demonstrated that the positive predictive value of mIBG score for identifying patients without SCD was 100% and therefore could be suitable to identify patients with HF who are at low risk

for SCD and do not require an ICD. The ADMIRE-HF study examined the predictive value of AdreView™ (Iobenguane I^{123} injection) imaging in 961 patients with New York Heart Association (NYHA) functional class II or III HF and LVEF ≤35% [Jacobson et al. 2010]. It evaluated the heart/mediastinum (H/M) ratio at 4 hours after tracer injection as a risk factor for HF progression, arrhythmic event (sustained ventricular tachycardia, cardiac arrest, or appropriate ICD discharge), or cardiac death. The H/M ratio of radioactivity uptake was a predictor for each of the individual event categories. An H/M ratio of <1.6 remained independently associated with cardiac events after adjustment for LVEF, b-type natriuretic peptide (BNP), and NYHA functional class. Based on these data, a recent decision-analytical model was developed to estimate the potential outcomes of using ^{123}I-*m*IBG to screen HF eligible for an ICD [O'Day et al. 2016]. Results of the analysis showed that ^{123}I-mIBG imaging could lead to a reduction of ICD utilization particularly in the 25-35% LVEF group. Below an LVEF value of 25%, the low number of patients expected to be at low risk based on the H/M ratio would indicate that it is not advisable to use this strategy in those with LVEF <25%.

In 2013, the Food and Drug Administration (FDA) approved GE Healthcare's AdreView™ (Iobenguane I^{123} injection) for the scintigraphic assessment of myocardial sympathetic innervation by measurement of the H/M ratio to assist in the evaluation of patients with NYHA class II or class III HF and left LVEF ≤35%. The label states that AdreView™ may be used to help identify patients with lower 1- and 2-year mortality risks, as indicated by an H/M ratio ≥1.6. The product information also highlights the limitations that AdreView™ utility has not been established for selecting a therapeutic intervention or for monitoring the response to therapy, nor for using the H/M ratio to identify a patient with a high risk for death.

All these findings have not yet been replicated prospectively, but represent a potentially powerful tool for reclassifying risk amongst patients previously thought to require device implantation. In particular, NYHA Classes II and III HF patients having a LVEF between 25% and 35% for whom the benefit of ICD implantation seems uncertain would benefit the most from an adequate staging of their cardiovascular risk and guidance of ICD implantation.

The most robust evidence for a direct impact of a test on overall health derives from a properly designed randomised comparative clinical study showing meaningful benefit for patient outcomes from test-guided care compared to Standard of Care (SoC).

5 STUDY OBJECTIVES AND PURPOSE

The primary and secondary objectives of the study are as follows:

Primary:

- To demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation in a population of NYHA class II and III HF patients with 25%≤LVEF≤35%. This will be achieved by comparing all-cause mortality observed in the AdreView™ -guided therapy group to that observed in patients receiving the 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.

Secondary:

- Compare the rate of hospitalisation and death related to major complications of ICD implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation) in patients randomised to the AdreView group with a heart-to-mediastinal ratio (H/M) ≥1.6 with patients in the SoC group with an H/M ≥1.6.

- Compare AdreView™-guided therapy to SoC therapy for:

  - The occurrence of cardiac death (composed of SCD, death due to cardiac arrhythmia, death due to HF, and death due to other cardiovascular causes).
  - The rate of hospitalisation for cardiovascular cause.
  - The rate of all-cause hospitalisation.
  - A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachyarrhythmias, SCD and resuscitated cardiac arrest.
  - The occurrence of syncope.
  - The clinical and healthcare resource utilisation data including, ICD implantation, all hospitalisations, treatment of adverse events (AEs), and AdreView™ administration.

- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). (AdreView™ group vs SoC).

Exploratory

- [redacted]

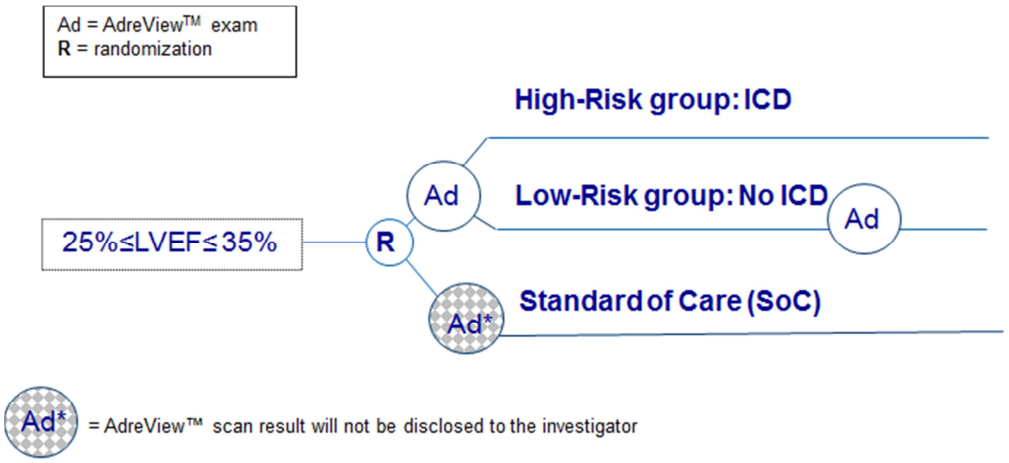
6 STUDY DESIGN

6.1 Overall Study Design and Plan

This is an event-driven Phase IIIb, multicentre, randomised, clinical study to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation, in NYHA class II and III HF patients with 25%≤LVEF≤35%, and in particular, for identifying patients who are at low risk for SCD and who would not benefit, or may suffer harm, from implantation of an ICD device.

An overview of study procedures is presented in Figure 1. Details of study procedures are provided in Section 9.

Figure 1 Study Diagram



Standard of Care (SoC) defined as the medical care as recommended by internationally accepted HF guidelines. AdreView™ scan results will not be disclosed to the investigator for the SoC group.

The study has been designed and endorsed by a Steering/Scientific Committee composed of world leaders in HF and arrhythmia management. Three committees will be formed in order to ensure proper scientific and ethical conduct of the study (see Section 9.7 for details):

- An Executive Steering Committee (ESC) will oversee the conduct of the study and will make recommendations to the Sponsor based on the outputs of the other committees.
- A Critical Events Adjudication Committee (CEAC) will adjudicate the study endpoints.
- A Data Safety Monitoring Board (DSMB) will oversee the overall study safety.

The endpoints in this study will be directly related to the health outcomes in both randomised groups. They will be standardised and assessed by an independent CEAC in a blinded fashion

in order to capture all those major events that are directly related to the efficacy of the strategies tested. The CEAC is comprised of experts in the field of clinical cardiology and arrhythmias, with extensive experience in the clinical care of HF patients and clinical trials in cardiology. The CEAC will set up their rules prospectively so that an objective adjudication can take place with the intent of capturing all those outcomes that are relevant in these patients. No members of the CEAC will be allowed to participate as site investigators, recruiting physicians or be directly involved in the care of study patients.

The DSMB will act as an independent committee overseeing all safety aspects of the study, and is comprised of experts with relevant experience in, cardiology, clinical trials safety, biostatistics and epidemiology. The DSMB members are independent of investigators entering or caring for patients in the study, are independent of the other study committees and are not involved in any other of the study activities than their role in the DSMB. The DSMB may recommend to the ESC and Sponsor termination of the study at any time should prospective ethical or safety guidelines not be met, or propose protocol amendments to ensure safety of study individuals. In addition, based on the regular or interim analyses performed, the DSMB may recommend to the ESC and Sponsor to re-calculate the sample size, or prolong or terminate the study should the power of the study become non-sufficient to achieve its objectives.

This study will be conducted at approximately 130 centres in the USA, Canada and Europe. At least 2354 patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least 2001 patients.

It is anticipated that patients will participate in the study until sufficient endpoints have been accrued which may correspond to an average of 2.75 to 3 years individual follow-up. The total study duration is expected to be approximately 6 years and the total required number of primary endpoint events observed is 247.

Only patients with stable heart failure who have been under guideline-directed optimal medical therapy for at least 3 months and have 25%≤LVEF≤35% will be considered for inclusion. Patients with LVEF >35% will be excluded. Patients must have 25%≤LVEF≤35% as measured in the previous 3 months before enrolment with no hospitalisations for HF or acute coronary syndrome during this period of time. In case these patients have a hospitalisation for HF or acute coronary syndrome, the LVEF measurement will only be valid if performed 40 days after this event. Patients without a LVEF measurement will have the test performed at screening. All LVEF images will be sent to the Sponsor. Study procedures will be performed as detailed in Section 9.

Patients with 25%≤LVEF≤35%, and meeting all other inclusion criteria and not meeting any of the exclusion criteria, will be randomly assigned to the AdreView™ group or the SoC group. All patients will be scheduled for an AdreView™ scan. The results of the AdreView™ scan in the SoC group will remain blinded to the investigator to avoid any influence in the decision of implanting an ICD. The results of the AdreView™ scan in the AdreView™ group will be known to the investigator and as such be used to assess their cardiovascular risk level and determine ICD implantation. Patients with AdreView™ H/M ratio <1.6 (high 1- and 2-year mortality risk) will undergo ICD device implantation. Patients with AdreView™ H/M ratio

≥1.6 (low 1- and 2-year mortality risk) will continue to receive guideline-directed optimal medical therapy according to clinical standard practice medical therapy and will not undergo ICD implantation. Patients in this later group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. Patients allocated to the SoC group will undergo ICD implantation and will be managed and followed up in accordance with internationally accepted HF guidelines.

Patients will attend follow-up visits at the rate determined by the investigator, in accordance with their clinical standard practice. However, a follow-up visit must take place at least every 6 months (an extra follow-up visit will be performed at 3 months after ICD implantation). All patients will also attend an end-of-study visit.

6.2 Stratification

To ensure appropriate distribution of variables that may affect the primary endpoint, the primary randomisation will be stratified based on the enrolling centre.

6.3 Study Timeframe

Patient recruitment is planned to start in 4Q 2015. The duration of this study will be dependent on the time taken to achieve a total of 247 primary endpoint events in the study. The expected duration of the study is 6 years (assuming a 32-month recruitment period and mean observational time per patient of 2.75 to 3 years).

6.4 Risks and Benefits to Patients

The study rationale and justification have been detailed in Section 4 above.

Current HF guidelines recommend implantation of ICD for primary prevention of SCD to reduce total mortality in NYHA class II and III patients with a LVEF≤35% after a minimum of 3 months of guideline-directed optimal medical therapy [Yancy et al. 2013]. However, there are still doubts about using the LVEF as the main criteria to decide on ICD implantation. [Al-Khatib et al. 2014] have suggested that perhaps devices for primary prevention of SCD should only be implanted in patients with LVEF<30%, thus identifying a population of patients with 30%≤LVEF ≤35% that might not benefit from ICD implantation. More recently Køber et al found that prophylactic ICD implantation was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care in patients with non-ischemic HF and LVEF ≤35% [Køber et al. 2016]. Furthermore, a pooled analysis of 1054 patients with class III HF included in SCD-HeFT, MADIT-II and DEFINITE trials, showed no significant survival benefit of ICD versus medical therapy [Barra et al. 2016]; while an ICD will prevent about 2 deaths per year for every 100 devices in patients with mild HF (NYHA class II) [Ponikowski et al. 2016]. Thus, it is expected that better risk stratification will lead to better patient selection improving the risk/benefit of ICD implantation.

The study will recruit patients with stable HF who have been under guideline-directed medical therapy for at least 3 months and have 25%≤LVEF ≤35%. Patients will be randomised to one of the 2 following groups. In one group, AdreView™ imaging will lead the decision of whether or not to implant an ICD and in the other it will not (the AdreView™ scan result will not be disclosed to the investigator). AdreView™ is a diagnostic radiopharmaceutical approved in the USA and several European countries for the identification of HF patients, NYHA class II and III with lower 1- and 2-year mortality risk. Patients randomised to the AdreView™ arm will have an ICD implanted within 45 days of randomisation if they are deemed to be at high risk according to the definition in Section 6.1 (AdreView™ H/M ratio [measured on an anterior planar image obtained at 3 hours and 50 minutes post-injection and calculated according to the instructions in the Imaging Manual] lower than 1.6). These patients should then face the same risks and benefits as those managed according to guidelines in the regular clinical setting.

Patients considered to be at low risk by AdreView™ imaging (i.e., those with a planar image H/M ratio≥1.6) will not receive an ICD, thus avoiding the exposure to complications; however they may face the risk that a potentially beneficial ICD implantation is withheld. GE Healthcare-sponsored study reports used for regulatory submissions (MBG311, MBG312 and MBG313; reports available upon request) have consistently showed a significant difference in all-cause and cardiac mortality between the high and the low risk groups in favour of the latter. These patients will also continue to receive the usual guideline-directed optimal medical therapy needed for their condition, including all the necessary follow-up visits and tests deemed necessary by the physician in charge. In addition, these patients will undergo a second AdreView™ H/M ratio determination 2 years after the first one in order to assess if their risk level has increased and ICD implantation is warranted. Moreover and as described in the protocol, the DSMB will regularly assess all safety aspects of the study.

Patients randomised to the SoC group will be treated in accordance to guidelines including having an ICD implanted, and therefore should then face the same risks and benefits as those managed according to guidelines in the regular clinical setting.

Planar imaging with AdreView™ is normally performed after intravenous administration of 370 MBq (±10%). Most ^{99m}Tc-labeled radiopharmaceuticals in common clinical use (with administered activities ranging from 370 to 1000 MBq) result in effective doses in the range of 2 to 6 mSv comparable to the doses received from other routinely performed diagnostic tests in radiology. The effective dose to an adult administered 370 MBq of AdreView™ is 4.8 mSv. The average background radiation dose per year in the United States is approximately 3 mSv and in Europe is approximately 2.4 mSv [Biological Effects of Radiation 2003] [Ionising Radiation 1996]. In recent procedure guidelines published by the European Association of Nuclear Medicine, the recommended dose of ^{123}I-mIBG for oncologic imaging studies in adults is 400 MBq [Bombardieri et al. 2003]. An administered ^{123}I-mIBG activity of 370 MBq has been demonstrated to allow consistently satisfactory planar and SPECT imaging with acceptable patient radiation dosimetry, which is particularly important for myocardial imaging studies in patients with heart disease, in whom the expected reduction in myocardial uptake may result in many uninterpretable SPECT studies if the lower dose historically employed for planar studies is used [Carrio 2001].

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Procedures for Site Selection

Investigational sites will be selected for this study based on high enrolment potential according to the protocol requirements and where a close working relationship with the nuclear medicine departments and electrophysiologists exists.

7.2 Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria:

(1) Patients ≥18 years of age at the time dated informed consent is obtained.

(2) Female patients must be pre-menarchal, surgically sterile (had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for more than 1 year), non-lactating, or, if of childbearing potential, a serum or urine pregnancy test with the results known prior to AdreView™ (Iobenguane I^{123} Injection) administration is negative.

(3) Patients willing and able to comply with all study procedures and a signed and dated informed consent is obtained before any study-procedure is carried out.

(4) Heart failure NYHA class II or III for symptoms, patients with ischemic or non-ischemic heart disease, eligible for ICD implantation as per each site's standard of practice.

(5) Non-ischemic dilated cardiomyopathy or ischemic heart disease of at least 3 months duration receiving guideline-directed optimal medical therapy.

(6) 25%≤LVEF≤35%, performed within 3 months before or at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted].
In case LVEF measurement is performed within 3 months before enrolment, measurement should be performed at least 40 days after a hospitalisation for HF or acute coronary syndrome (including myocardial infarction), and to be valid, method of measurement should be in accordance with the protocol and the imaging exam should be made available to the Sponsor in digital format.
In case several valid LVEF measurements are available, the closest to enrolment will be used for inclusion determination.

(7) Clinically stable HF in the medical judgment of the investigator (i.e., no significant changes in medication, no worsening of symptoms, no unscheduled visits to the doctor's office) for the past 30 days and no hospitalisation for HF or acute coronary syndrome (including myocardial infarction) in the past 40 days.

(8) Reasonable expectation of meaningful survival for at least 1 year.

7.3 Exclusion Criteria

Patients must be excluded from participating in this study if they meet any of the following criteria:

(1) Patients with existing ICD or patient having an indication of ICD implantation for secondary prevention of SCD.

(2) Hospitalisation for HF or for acute coronary syndrome in the previous 40 days.

(3) Patients where a cardiac resynchronisation therapy (CRT) is planned or indicated

(4) Other indication for placement of device (sustained ventricular tachycardia, resuscitated sudden death, need for atrioventricular pacing).

(5) NYHA class I or class IV symptoms at the time of study entry.

(6) American College of Cardiology-American Heart Association (ACC-AHA) class III or class IV (unstable) angina.

(7) Patient with chronic renal insufficiency defined as serum creatinine ≥3 mg/dl (or ≥265.2 μmol/L).

(8) Known or suspected hypersensitivity/allergy to Iobenguane or to any of the excipients in AdreView™ (Iobenguane I^{123} Injection).

(9) Patient who is pregnant or plans to become pregnant within 2 weeks after AdreView™ (Iobenguane I^{123} Injection) administration.

(10) Patient who has used any medication in the 2 weeks before AdreView™ (Iobenguane I^{123} Injection) that could interfere with the test: e.g., but not limited to amitriptyline or derivatives, imipramine or derivatives, other antidepressants or drugs known or suspected to inhibit the norepinephrine transporter, antihypertensives that deplete norepinephrine stores or inhibit reuptake, sympathomimetic amines or cocaine.

(11) Patients that have a medical condition that could interfere with the AdreView™ test (e.g., but not limited to left ventricular assist device, or prior heart transplant).

(12) Patients who participated in a clinical study involving a drug or device within 30 days prior to study entry and patients participating in any other clinical study.

(13) Patients having serious non-cardiac medical condition associated with significant elevation of plasma catecholamines, including pheochromocytoma.

(14) Patients with a clinical diagnosis of (or being treated for) Parkinson's disease or Multiple System Atrophy.

(15) The patient has participated in a research study using ionizing radiation in the previous 12 months.

(16) Patients previously randomized in this study.

7.4 Withdrawal and Termination Criteria

7.4.1 Patient Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the Sponsor may review the safety data for trends and signals that would indicate the need for withdrawal of a patient.

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw patients from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the patient, or in the case of lack of co-operation.

Should a patient decide to withdraw after administration of AdreView™, or should the investigator(s) decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given of why the patient is withdrawing or being withdrawn from the study. As this is an intention to treat analysis, all patients should be followed for the primary endpoint of all-cause mortality if at all possible. ICD crossover or having a secondary endpoint is not a reason to withdraw from the study.

The reason for withdrawal must be noted in the electronic Case Report Form (eCRF). If the reason for withdrawal is a serious adverse event (SAE), monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. The reason for withdrawal must be noted in the eCRF. If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. Patients withdrawing prior to completing the study may be replaced.

7.4.2 Study or Site Termination

The DSMB may recommend to the ESC an early termination of the study based upon their review of the safety signals. This board will meet at pre-defined intervals. Any recommendation for an early termination will be promptly communicated to the ESC that will evaluate the report and evidence provided by the DSMB. In the case that this recommendation is not supported by the ESC, both committees will meet to reach a final definitive conclusion. The ESC will have the final say. Once a final opinion is endorsed by the ESC, it is communicated without delay to the Sponsor that will take appropriate action.

This is an event-driven study and the ESC can propose to terminate the study early if sufficient events (as calculated prospectively in this protocol) are reached before the expected end of the study. Similarly, the ESC can propose to terminate the study early if it is unlikely that a sufficient number of events (as calculated prospectively in this protocol) will be reached before the expected end of the study. Finally, the ESC can propose to prolong the study if it is unlikely that a sufficient number of events (as calculated prospectively in this protocol) will be

reached before the expected end of the study but could be reached through an extension that the ESC deems reasonable.

The Sponsor reserves the right to terminate the study at any time. The Sponsor also reserves the right to discontinue participation of a study site at which no patients have been enrolled within 3 months of site initiation or in case of safety concerns or severe protocol violations.

8 TREATMENT OF PATIENTS

8.1 Investigational Medicinal Product (IMP)

8.1.1 AdreView™ (Iobenguane I^{123} Injection)

After randomisation to either the AdreView™ group or the SoC group, all patients will receive at least one intravenous injection of 10 mCi (370 MBq) of AdreView™. A ±10% tolerance of the nominal dose will be allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) in accordance with the Package Insert/Summary of Product Characteristics/Investigator's Brochure (IB). AdreView™ will be 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. An administration volume of up to 15 mL may be used at sites where there are logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.

Patients being allocated to the AdreView™ low-risk group will receive a second injection of AdreView™ and planar /SPECT imaging 2 years (±30 days) after the first one. If any of these patients voluntarily withdraw prior to completion of the study they will be offered this second AdreView™ scan prior to withdrawal being effective.

Refer to the Package Insert/Summary of Product Characteristics/IB and Appendix 15.2 for further detail.

8.1.2 Adjunctive Medication: Thyroid Blockade

Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

Each investigator is responsible for obtaining the appropriate thyroid blockade agent and for its administration in accordance with national and local regulations and guidelines. The type of thyroid blockade agent, time of administration, and quantity of compound will be recorded in the eCRF.

8.1.3 AdreView™ Accountability

Each investigator is responsible for ensuring that deliveries of AdreView™ and other study materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol.

All AdreView™ containers (opened, unopened, or empty) must be returned to the Sponsor or destroyed on site after the study and overall drug accountability have been completed by the Sponsor or representative. A list of AdreView™ doses and other materials that were returned, or destroyed, must be prepared and signed by the principal investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

8.1.4 Comparator

No comparator imaging modality(ies) will be used. The main comparator will be medical SoC as described in Section 6.1.

8.1.5 Registration of Investigational Medicinal Product Complaints

In the event of AdreView™ complaint (e.g., breakage, leakage, particulate matter, discoloration), the investigator or recipient of AdreView™ is requested to report the problem on the AdreView™ shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form). This should be promptly forwarded to the person indicated on the shipping documentation. Once received, the Clinical Supplies Manager will register the complaint and determine if the complaint is minor or significant according to Sponsor procedures. All complaints will be followed-up and the appropriate action will be implemented according to Sponsor procedures.

8.2 Method of Numbering Patients and Assigning Patients to Treatment Groups

A unique allocation number will be assigned to each patient in successive order of entering the study after signing the informed consent document at each centre. Patients who fail one or more inclusion/exclusion criteria may be re-screened at a later date and, if subsequently found to be eligible, randomized into the study. No patient may be randomized into the study more than once (i.e., patients withdrawn after randomization may not be re-screened). The allocation number will be unique for each patient in the study and will consist of 7 numbers in total: 3 numbers for the centre identification and 4 numbers for the patient identification at the centre (e.g., 0020001: first patient in centre No. 2). Please see the section on randomisation, Section 9.2.

Once an allocation number is assigned, it cannot be reassigned even if the patient is deemed ineligible or withdraws consent. To preserve the scientific integrity of the study, numbers must be assigned in numeric order.

Patients enrolled in the trial will be randomly assigned to the AdreView™ group (will receive AdreView™) or the SoC group (will receive AdreView™, however the results must remain blinded to the investigator). Allocation to the enrolment groups, including randomization, will be performed centrally (via an interactive web response system [IWRS]) by the Sponsor or contract research organisation (CRO).

No patient will be administered AdreView™ before it has been determined that the patient meets the study's inclusion/exclusion criteria and a signed and dated informed consent has been obtained.

8.3 Selection of Doses and Timing

All patients will receive at least one intravenous injection of 10 mCi (370 MBq) of AdreView™. A ±10% tolerance of the nominal dose will be allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) in accordance with the Package Insert/Summary of Product Characteristics/IB (refer to Section 8.1).

AdreView™ will be 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. An administration volume of up to 15 mL may be used at sites where there are logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.

Patients allocated to the AdreView™ low-risk group will receive a second injection of AdreView™ 2 years (±30 days) after the first one. Should the H/M ratio from the second scan fall under 1.6 and the patient is willing and eligible for ICD implantation, he/she could receive an ICD. If any of these patients voluntarily withdraw prior to completion of the study they will be offered this second AdreView™ scan prior to withdrawal being effective.

AdreView™ doses and imaging times have been selected following clinical experience and technical information approved by the Health Authorities in the USA and Europe.

8.4 Blinding and Measures to Minimise Bias

Neither patients nor site personnel (including the on-site AdreView™ scan reviewer) can be blinded to group assignment. Sites must know whether patients are randomised to the AdreView™ or SoC groups in order to use the results of the scans in the AdreView™ group. For patients in the randomised SoC group the investigator will remain blinded to the results of the AdreView™ scan.

Both the DSMB and the CEAC will review patient data while blinded to enrolment group. The DSMB could, should it be regarded as necessary for their analysis, also review patient data in an unblinded fashion.

8.5 Prior and Concurrent Therapy

Any medications taken by the patient within 30 days before and up to the end of study visit will be recorded in the eCRF along with the indication and dosage, including but not restricted to guideline-directed optimal medical therapy. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognised dictionary of medical codes.

Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.

As stated in the exclusion criteria, patients will not be allowed to take any medications known or suspected to interfere with AdreView™ imaging as per Package Insert (or Summary of Product Characteristics or IB as applicable) for at least 5 half-lives prior to administration of AdreView™. The investigator will be responsible for assessing the patient's medication in order to determine whether the medication should be withdrawn for the required period. In the case of a patient requiring medications that can interfere with AdreView™ imaging and where the clinical status does not allow temporary withdrawal of the medication, the investigator may elect to withdraw the patient from the study on safety grounds.

8.6 Treatment Compliance

Patients will receive AdreView™ under direct supervision of study personnel. Information concerning the administration of AdreView™ (i.e., date, time, activity, and volume administered) will be checked and the code and volume per administration will be recorded in the patient's eCRF. Doses administered outside of specific dose requirements or defined range must be reported as protocol deviations (see Section 13.3).

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarised in the Study Schedule of Events (Table 1).

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [k]
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographic Information	X						
Medical/Surgical History	X			X	X		X
Concomitant Medications [b]	X			X	X		X
Pregnancy Test [c]	X		X			X	
Pre-Inclusion Events	X						
Physical examination (complete)	X						
Brief Physical examination				X	X		X
Blood samples for clinical laboratory evaluation	X						
Vital signs [d]	X			X	X		X
ECG	X						
Check LVEF values within the previous 3 months or perform LVEF assessment. [e]	X						
Assignment to study group		X					
AdreView™ Administration [f]			X			X	
Injection site monitoring			X			X	
Image Acquisition (Planar and SPECT) [e, g]			X			X	
ICD Implantation (if applicable) [h]			X				
ICD interrogation (if applicable) [i]				X	X		X
AEs, SAEs and AdreView™-emergent AEs[j]	X	X	X	X	X	X	X
Data collection pertaining to primary and secondary endpoints			X	X	X	X	X

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [k]

*All procedures listed do not necessarily need to be performed during a single day

a Signed and dated informed consent must be obtained before eligibility assessments, including pregnancy test, are commenced.

b Recorded up to 30 days before screening. Investigators should record all guideline-directed optimal medical therapy. Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.

c A serum or urine pregnancy test will be performed for all women of childbearing potential.

d Before vital signs are measured, the patient should be resting for at least 5 minutes. The same arm and position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contra-lateral to the site of AdreView™ administration whenever possible.

e Acceptable methods of LVEF assessment are radionuclide or contrast ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D 2D echocardiography (Simpson's or multidisc method or equivalent only). Image files will be sent to the Sponsor.

f AdreView™ will be administered to all patients. First AdreView™ administration should be performed in the 15 (+7) days post-randomisation. For the low-risk cohort only, a second AdreView™ administration should be administered at 2 years (±30 days) post-randomisation, unless patient withdraws prior to study termination or has already received an ICD. In this case the second AdreView™ scan will be offered before withdrawal becomes effective. Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

g At 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of planar images, and whenever possible followed by SPECT acquisition, according to the imaging manual. Patients with LVEF 25% to 35% with an H/M ratio ≥1.6 will have a second AdreView™ scan at 2 years (±30 days) post-randomisation.

h Patients in the randomised AdreView™ group who are assessed as high risk, and patients in the SoC group according to the standard of care in each investigational site derived from the local implementation of internationally accepted HF guidelines. ICD implantation should be performed according to clinical practice and should be performed within 45 days after randomisation.

i ICD interrogation does not need to be performed on the same day as the corresponding follow-up visit. ICD interrogation may be done remotely within ±5 days of the corresponding follow-up visit.

j AdreView™-emergent AEs are defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

k Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

9.1 Screening/Enrolment Visit

Signed and dated informed consent must be obtained from all patients prior to any screening procedures. All patients must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.

It is not necessary for all procedures to be performed during a single day.

At the screening/enrolment visit, LVEF function determination will be performed in cases where a previous LVEF measurement is not available. If there is a previous LVEF measurement performed within 3 months of enrolment, the investigator will check that this measurement was performed when the patient had no hospitalisations for HF or acute coronary syndrome, or if such hospitalisation happened then the LVEF measurement was performed 40 days after the event. Acceptable methods for LVEF determination are as follows: radionuclide ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D or 2D echocardiography (Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted). LVEF images will be sent to the sponsor in electronic format.

The following parameters will be collected:

- Demographics
- Medical history
- Concomitant medications, including guideline-directed optimal medical therapy. Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.
- Vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry)
- Blood samples for serum chemistry and haematology and BNP or N-terminal pro b-type natriuretic peptide (NT proBNP) determination will be collected (according to Table 2)
- Physical examination will be performed
- All female patients will undergo a serum or urine pregnancy test unless surgically sterile or post-menopausal
- A 12-lead ECG will be performed
- Collection of pre-inclusion events will commence

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances. Any exceptions to protocol-specified requirements will be considered as protocol deviations.

9.2 Randomisation

Randomisation to the AdreView™ or SoC groups will be done remotely through an electronic data capture system. Once the investigator has reviewed and properly entered the requested data, the electronic system will allocate the patient to the appropriate cohort should the patient be allowed to pursue the study. The primary randomisation is to one of 2 treatment methods in a 1:1 ratio stratified by enrolling centre.

Patients with 25%≤LVEF≤35% will be randomly assigned to the AdreView™ group or the SoC group via an IWRS. They will be scheduled for an AdreView™ scan to be performed within 15 (+7) days post-randomisation.

The following procedures will be performed and parameters will be collected:

- Assignment to study group
- Collection of AEs and SAEs will commence, as well as study endpoints.

9.3 Post-Randomisation Procedures

All female patients (unless pre-menarchal, surgically sterile or post-menopausal) will undergo a serum or urine pregnancy test on the day of and prior to AdreView™ administration. AdreView™ dosing will only commence if the result is negative.

AdreView™ will be administered to all patients.

The first AdreView™ administration should be performed in the 15 (+7) days post-randomisation. Starting at 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of anterior planar images of the thorax, and whenever possible these will be followed by a SPECT acquisition. Details of the acquisition and transmission of images to the Sponsor are provided in the study Imaging Manual.

Only those patients allocated to the AdreView™ arm will have the results of the scan (H/M ratio calculated on an anterior planar image obtained at 3 hours and 50 minutes for 10 minutes, and with regions placed following the standard quantification method according to the Imaging Manual) available to make a decision on the need for implantation of an ICD. In patients allocated to the SoC group, the investigator will remain blinded to the results of the AdreView™ images and any information derived from them in order not to influence the decision to implant or not implant an ICD.

Patients in the AdreView™ arm who are deemed at high-risk for all-cause and cardiovascular mortality (H/M ratio <1.6 as defined in Section 6.1) will undergo ICD device implantation. ICD implantation should be performed within 45 days of randomisation. Patients deemed to be at low risk (H/M ratio ≥1.6 as per Section 6.1) will continue to receive guideline-directed optimal medical therapy but will not undergo ICD implantation. In the low risk group, a second AdreView™ scan will be performed at 2 years following the first scan, or in case of early withdrawal, prior to this withdrawal being effective.

Patients randomly allocated to the SoC group will undergo ICD implantation and will be managed and followed up in accordance with internationally accepted HF guidelines. ICD implantation should be performed within 45 days of allocation to the SoC group. The results of the AdreView™ scan will remain blinded to the investigator to avoid any influence regarding patient management. AEs, SAEs and AdreView™-emergent AEs will be recorded.

All data related to primary and secondary endpoints will be collected.

Injection site monitoring will be performed before and after injection (with findings recorded pre-administration, 15 minutes post-administration, and at discharge from the imaging suite).

9.4 Follow-Up

After randomisation, all patients will be followed up according to medical practice. However a follow-up visit will occur at least every 6 months. Additionally, all patients in whom an ICD is implanted will also have a follow-up visit 3 months after the procedure has taken place.

Patients will be followed up for the specified time and events and safety data will be collected throughout the entire study.

For those patients whose clinical status worsens during the follow-up period, the investigator will decide on the necessity for ICD implantation based entirely on the risk/benefit to the patient and patient eligibility for ICD implantation.

9.4.1 Follow-Up Visit at 3 months (Only Patients Having Received ICD)

A follow-up visit at 3 months post-ICD implantation for those patients that had an ICD fitted will take place. The following parameters will be collected at this visit:

- Medical/Surgical history
- Concomitant medication
- A brief physical examination will be performed (as defined in Section 10.2.4)
- Vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry)
- All data related to primary and secondary endpoints
- AEs, SAEs and AdreView™-emergent AEs
- ICD interrogation; may be performed remotely within ±5 days of follow-up visit.

9.4.2 Follow-Up Visits (All Patients)

Patients will attend follow-up visits at the rate determined by the investigator, in accordance with their clinical standard practice. However, a follow-up visit must take place at least every 6 months.

The following data will be recorded:

- Medical history
- Vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry)
- Brief medical examination data (as defined in Section 10.2.4)
- Concomitant medications
- All data related to primary and secondary endpoints.
- AEs, SAEs and AdreView™-emergent AEs.
- ICD interrogation (for those patients with an ICD); may be performed remotely within ±5 days of follow-up visit.

9.5 Second AdreView™ Administration

Patients in the low-risk AdreView™ group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. All female patients will undergo a serum or urine pregnancy test unless pre-menarchal, surgically sterile or post-menopausal prior to this scan. Should the H/M ratio fall under 1.6 and the patient is willing and eligible for ICD implantation, he/she should receive an ICD. Should the patient withdraw prior to study termination the second AdreView™ scan will be offered prior to said withdrawal being effective.

- AEs, SAEs and AdreView™-emergent AEs will be recorded
- All data related to primary and secondary endpoints will be collected
- Injection site monitoring will be performed before and after injection (with findings recorded pre-administration, 15 minutes post-administration, and at discharge from the imaging suite)

9.6 End of Study Visit

This will be an event-driven study. Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

If a patient discontinues prematurely, he/she will attend an end of study visit at that time. As this is an intention-to-treat analysis, all patients should be followed for the primary endpoint of all-cause mortality if at all possible.

The following parameters will be collected:

- Medical history (with identification of study end-points)
- Concomitant medications
- Vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry)
- A brief physical examination will be performed.
- AEs, SAEs and AdreView™-emergent AEs
- All data related to primary and secondary endpoints
- ICD interrogation (for those patients with an ICD); may be performed remotely within ±5 days of follow-up visit.

9.7 Study Committees

The study was designed and endorsed by a Steering/Scientific Committee of worldwide recognised experts in the field of HF and arrhythmia management.

Three main committees will be derived from this Steering/Scientific Committee. All 3 committees will be independent from the Sponsor. Other committees, e.g., Publication Committee, may be set-up by the ESC, if required. It is expected the committees will meet regularly during the conduct of the study.

(i) Executive Steering Committee

The ESC is responsible for the scientific and technical aspects of the study conduct. It will be comprised of qualified physicians, independent from the Sponsor, who are recognised experts in the field of HF management worldwide. The ESC will review and finalise the protocol and its amendments. The ESC has the authority to convene meetings of any of the study committees. The ESC will review promptly any recommendation made by the DSMB with regards to early termination, protocol amendments, results of any interim analysis or prolongation of the study as needed. The ESC will make the final recommendation that will be communicated promptly to the Sponsor and the reasons shall be clearly documented.

The ESC will work according to a charter of rules approved by both the ESC members and the Sponsor.

(ii) Critical Events Adjudication Committee

The CEAC will adjudicate the study endpoints in a blinded fashion. It will be comprised of qualified physicians who are experts in the field of cardiac failure and have the necessary relevant experience in clinical trials and adjudication of efficacy events, and who are independent from the Sponsor. The CEAC will be composed of 1 Chair and 3 members. The Chair will represent the CEAC in front of the other Committees and the Sponsor. All CEAC members will review events generated by the sites. Each event will be reviewed by 3 members out of the 4. All events will be adjudicated as all 3 members agree on the outcome after reviewing all available clinical information. There are 4 possible outcomes:

1. The event is a study endpoint and there is a unanimous agreement on its classification: The event is validated.

2. There is a unanimous agreement that the event is not a study endpoint.

3. More information is needed: The CEAC will request more information to the site via the Sponsor's designated monitor.

4. The event could be a study endpoint however there is a disagreement on its classification.

In case additional information is requested, a second review with the additional information received from the site will aim at classifying the event into the 1st or 2nd outcome as above displayed.

All cases that cannot be unanimously adjudicated during the 2 steps described above, or where there is a disagreement, will be reviewed in common to get a final decision.

Whenever possible all adjudications will be done remotely using electronic systems that comply with all legal and regulatory requirements.

The CEAC decisions will be based on members' blinded review of the data provided by the investigators (via a CRO). Data provided may be: AE, SAE, eCRFs, hospitalisation discharge, etc. and specific documents the CEAC member may request.

The CEAC will work according to a charter of rules approved by CEAC members, the ESC and Sponsor.

(iii) Data Safety Monitoring Board

An independent DSMB will meet periodically, or as needed, to review and evaluate any safety issues that may arise during the course of the study.

The DSMB will consist of 5 members: 1 Chair, 3 members and 1 independent statistician, with expertise in the management of patients with HF as well as safety monitoring in clinical studies. The Chair's additional activities include representing the DSMB in front of the other committees and the Sponsor, including presentations at the ESC as requested. Under no

circumstances will any of the members be allowed to participate in the study conduct (other than the actives related to the DSMB).

The ongoing study safety data (blinded to study group) will be transmitted to the DSMB (statistician) by Sponsor or CRO on a regular basis as defined in the DSMB Charter. The DSMB will carry out periodic data review and will inform the ESC and the Sponsor on any safety concerns. Should unblinding be required, the DSMB will request authorisation to the ESC and Sponsor before proceeding.

During the course of the trial the DSMB may recommend to the ESC and Sponsor to perform interim analyses (see Section 12.7).

The DSMB may recommend to the ESC and Sponsor termination of the study at any time should prospective ethical or safety guidelines not be met, or propose protocol amendments to ensure safety of study individuals. In addition, based on the regular or interim analyses performed, the DSMB may recommend to the ESC and Sponsor to re-calculate the sample size, or prolong or terminate the study should the power of the study become non-sufficient to achieve its objectives.

The DSMB will work according to a charter of rules approved by DSMB members, the ESC and the Sponsor.

10 EFFICACY AND SAFETY VARIABLES

10.1 Efficacy Assessments

10.1.1 Primary Endpoint

- The primary endpoint will be all-cause mortality

10.1.2 Secondary Endpoints

10.1.2.1 Key Secondary Endpoints

- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). (AdreView Low-risk group vs SoC H/M ≥1.6).

- Cardiac death (composed of SCD, death due to cardiac arrhythmia, death due to HF, and death due to other cardiovascular causes)

- The rate of hospitalisation for cardiovascular cause.

- The rate of all-cause hospitalisation.

- A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachyarrhythmias, SCD and resuscitated cardiac arrest.

10.1.2.2 Additional Secondary Endpoints

- The occurrence of syncope.

- The clinical and healthcare resource utilisation data including, ICD implantation, all hospitalisations, treatment of AEs, and AdreView™ administration.

- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks explantation). (AdreView™ group vs SoC).

The above listed primary and secondary endpoints (except those only economic) will be reviewed and validated by the CEAC for all patients.

10.1.3 Exploratory Endpoint

- [redacted]

10.1.4 Standard of Truth, Comparator or Reference Imaging

This is an outcome study where 2 clinical strategies will be compared. Therefore there is no standard of truth (SOT) per se, but a group of cardiac and other health outcome-related events that will be considered the primary efficacy endpoint upon which the performance of each strategy will be compared. There is currently no other approved diagnostic agent to detect myocardial innervation in North America or Europe; therefore there is no direct comparator to AdreView™. There is therefore no reference imaging.

10.1.5 Image Interpretation and Correlation with Standard of Truth

AdreView™ images will be analysed according to standard procedures as laid out in the Imaging Manual. Planar images will be analysed as per the FDA-approved label (i.e., USA version Package Insert) where regions of interest (ROIs) will be placed in mediastinum and whole heart to calculate H/M ratio by nuclear medicine department personnel. These Imaging Manual instructions (based on the USA version of the Package Insert) agree with procedures and/or guidances approved by the Health Authorities for all countries in which the product is approved for scintigraphy assessment of sympathetic innervation of the myocardium. If sites from any additional countries are added to the study, they must follow the instructions in the Imaging Manual for acquisition of images and calculation of H/M, regardless of any potential differences with local guidances that may exist. The GE-122-020 Imaging Manual will describe image acquisition (planar and SPECT), processing (planar only) and analysis (planar only). AdreView™ planar image analysis and quantification will be performed on-site and there will be no central blinded reads. Results of the H/M ratio will be correlated with the patient's clinical outcome.

All AdreView™ planar and SPECT images will be sent to the Sponsor's central laboratory for further analysis. SPECT images will be analysed in a blinded manner. Results of the quantification of the regional distribution will be compared with clinical parameters (i.e., ECG, NYHA, LVEF, etc.) and efficacy endpoints, to assess for any trends in order to generate working hypothesis for future studies. Analysis of SPECT images collected during the study will be done in an exploratory manner and may be reported separately.

10.2 Safety Assessments

The investigator(s) and the Sponsor/CRO will review the safety data. The following safety data will be collected and evaluated:

- Clinical laboratory parameters: serum biochemistry and haematology (Table 2).

- Vital signs: systolic/diastolic blood pressure, respiratory rate, heart rate, intermittent pulse oximetry.
- 12-lead ECG.
- Physical examination (complete and brief).
- Injection site monitoring before and after injection (with findings recorded pre-administration, 15 minutes post-administration, and at discharge from the imaging suite)
- Pre-randomisation events.
- Post-randomisation events (AEs, SAEs, and AdreView™-emergent AEs).

Pre-specified normal limits for vital signs and ECG intervals are provided in Section 15.3. Interpretation and follow-up of abnormal results should be conducted in conjunction with the clinical situation of the patient. Normal limits for clinical laboratory parameters are set by the local laboratory used.

10.2.1 Clinical Laboratory Evaluation

Clinical laboratory parameters assessed in this study are displayed in Table 2.

Table 2 Clinical Laboratory Parameters

Serum Biochemistry	Haematology
Chloride Urea nitrogen Creatinine Bicarbonate Sodium Potassium Glucose Alkaline phosphatase Aspartate transaminase Alanine transaminase Bilirubin (Total) Brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT proBNP)	Haematocrit Haemoglobin Platelet count White blood cell (WBC) count Lymphocyte % Troponin ST2 and Gal 3 biomarkers (if available for on-site determination).

The signed and interpreted laboratory results will be kept together with the patient's eCRF (paper or electronic) as supplemental pages at the site.

Blood samples will be obtained for assessment of serum biochemistry and haematology at enrolment (Table 1). Samples will be analysed at the local laboratory (for parameters, see Table 2). All blood samples will be processed and handled per standard laboratory procedures.

10.2.2 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry) will be monitored according to the study schedule of events, Table 1. Before vital signs are measured, the patient should rest for at least 5 minutes (if possible). The same position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the same arm contra-lateral to the site of AdreView™ administration whenever possible.

10.2.3 Electrocardiograms

A standard 12-lead ECG will be obtained at screening (Table 1). All ECG recordings will be read at the investigational site.

10.2.4 Physical Examination

A qualified physician with experience in the management of HF patients will conduct physical examinations at screening and at follow-up and end-of-study visits. The same individual should conduct the physical examination at all required time points whenever possible. A complete physical examination should be completed at screening/entry while a brief one should be sufficient for follow-up visits unless the physician in charge considers otherwise based on the clinical status of the patient. The complete physical examination will include recording an assessment for the presence of abnormalities of the following: general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae, cardiovascular system, back and spine, abdomen, extremities, injection site, lymph nodes, and neurological exam. The brief physical examination will include general appearance, cardiovascular, and neurological exam. All additional examinations will be conducted by the physician in view of the clinical status of the patient and the findings in the brief physical examination.

In the event that *new* abnormal physical findings and *worsening* abnormal physical findings are encountered during the study, these terms are defined as follows: a new abnormal physical finding is defined as one that occurs when a patient's normal baseline physical examination becomes abnormal post-baseline. A worsening abnormal physical finding is defined as one that occurs when a patient's abnormal baseline physical examination becomes worse post-baseline. Such events must be recorded as AEs/SAEs.

10.2.5 Injection Site Monitoring

Injection site monitoring will occur before AdreView™ injection and throughout the post-administration period with findings recorded pre-administration, 15 minutes post-administration, and at discharge from the imaging suite.

Abnormal injection site findings include, but are not limited to: haematoma, dermatitis, urticaria, extravasation, bleeding, redness, phlebitis, and infection. Any abnormal finding that is new or represents a worsening from baseline is an AE.

10.2.6 Study Endpoints

Study endpoints will be documented and adjudicated according to the CEAC Charter.

A significant overlap between safety and efficacy events is expected. The study aims at comparing 2 prospective cohorts identifying a significant difference in patient outcomes. These outcomes will be composed of clinical events that usually conform to the definition of AEs and SAEs (i.e., death or prolonged hospitalisation). A set of specific criteria will be agreed upon by the CEAC defining efficacy events that will be used to identify those events that will require adjudication by the committee.

All AEs will be collected, analysed and (reported independently of their possible adjudication as an efficacy event), and according to Good Clinical Practice (GCP), legal and regulatory requirements.

10.2.7 Adverse Events

As per International Conference on Harmonisation (ICH)-GCP, an AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to that product.

The patients will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., “How do you feel?”). The patients will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for 30 minutes after dosing. Treatment of SAEs (defined in Section 10.2.8) should be primarily supportive of vital functions.

Laboratory AE Evaluation

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the patient. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient’s condition (e.g., ordering a WBC differential to help characterise a high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit).

10.2.8 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

(*Other important medical events are those that may not result in death, be life-threatening, or require hospitalisation, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the patient and may require medical intervention to prevent one of the outcomes listed above.)

Investigators must ensure that all SAEs are reported to the Sponsor/CRO within 24 hours.

The CRO will support the Sponsor in reporting all SAEs to local health authorities, Independent Ethics Committees (IECs)/Institutional/Independent Review Boards (IRBs) and investigators as required by local regulations and Sponsor/CRO Standard Operating Procedures (SOPs).

10.2.9 Other Significant Adverse Events

Clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of AdreView™, dose reduction or significant additional concomitant therapy), other than those reported as SAEs, will be reported and evaluated as other significant AEs.

10.2.10 AdreView™-Emergent Adverse Events

Reported adverse reactions associated with AdreView™ have been very uncommon (<1% in almost all cases). Per the IB, the only adverse reactions that occurred with a frequency >1% were associated with the injection site (1.3%). The other most common reactions were flushing (0.3%) and headache (0.4%). The adverse reactions were predominantly of mild to moderate intensity. Rare undesirable effects that have been reported include blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions.

An AdreView™-emergent AE is defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

Both the investigator(s) and Sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that AdreView™ caused the event.

Causal relationship

The relationship of an AE with AdreView™ will be assessed and reported by the investigator as:

- Reasonably related to study drug ("Reasonable cause"): - A causal relationship between AdreView™ and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not reasonably related to study drug ("Not reasonable cause"): - A causal relationship between AdreView™ and an AE is not a reasonable possibility.

A suspected adverse reaction is an AE where reasonable possibility exists for causality between AdreView™ and the AE.

Expectedness

All AdreView™-emergent AEs will be assessed, by the Sponsor (Global Pharmacovigilance), as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the applicable safety information included in the IB for AdreView™.

Unexpected: An unexpected AdreView™-emergent AE is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable safety information included in the IB.

Expected: An expected AdreView™-emergent AE is a reaction which is consistent with the applicable safety information included in the IB.

10.2.11 Adverse Event and Serious Adverse Event Reporting

All AEs should be recorded using acceptable diagnoses, if possible. If an AE has already been reported (by the investigator to the Sponsor/CRO) it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild: Tolerable.

Moderate: Interferes with normal activity.

Severe: Incapacitating (causes inability to perform usual activity or work). The investigator will be instructed to closely monitor each patient who experiences an AE (whether ascribed to AdreView™ or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the Sponsor/CRO according to a well-recognised dictionary of medical codes (Medical Dictionary for Regulatory Activities [MedDRA]).

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in a study, and for SAEs at database lock.

SAEs must be notified to the Sponsor/CRO within 24 hours. Details regarding how to notify the Sponsor/CRO of SAEs and contact details for any protocol or safety-related questions will be provided in a separate document.

Patients enrolled at sites in the European Union will be provided with a Clinical Trial Participant card at the time of enrolment. This card will list contact details for the investigator and for GE Healthcare medical emergency cover services (Clinical Trial Emergency Contact Service [CTECS]). The CTECS provides 24 hour, 7 day a week emergency cover service for healthcare professionals to seek advice on study-related medical questions or problems should a medical emergency arise and the investigator is not available.

10.2.12 AdreView™-emergent Serious Adverse Event Reporting

Any AdreView™-emergent SAE must be forwarded immediately by the initial recipient at the Sponsor/CRO to the Global Pharmacovigilance mailbox:

[redacted]

10.2.13 Urgent Safety Measures

In accordance with the principles of GCP as laid out in ICH E6, the investigator(s) has/have primary responsibility for assuring patient safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IEC/IRB approval/favourable opinion.

The investigator may take appropriate urgent safety measures in order to protect the patients of a clinical study against any immediate hazards to their health or safety. However, the investigator must inform the Sponsor/CRO within 24 hours of having taken such measures.

The Sponsor in turn shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IEC/IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the Sponsor/CRO using the SAE contact numbers listed in Section 10.2.11 within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

10.2.14 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to AdreView™ exposure of pregnant women and/or foetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all patients following exposure to AdreView™.

Female study patients: The study patient must be advised by the investigator to inform him/her immediately if she suspects she may be pregnant and believes conception occurred within 72 hours of AdreView™ administration.

Male study patients: The study patient must be advised by the investigator to inform him/her immediately if he suspects his partner became pregnant within 72 hours after AdreView™ administration.

When a study patient reports a pregnancy (post-AdreView™ administration) to the investigator, a pregnancy test should be arranged for the study patient (or their partner) by the investigator within 7 days of the pregnancy being reported.

The investigator must inform the Sponsor/CRO within 24 hours of receiving positive pregnancy test results using either a copy of the relevant eCRF page (demography or AE) or via email. The investigator should include an estimated date of conception when communicating with the Sponsor/CRO.

10.3 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For eCRFs, data will be entered by trained site personnel with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data and should be signed by the investigator(s) (e.g., results of physical examinations, vital signs testing, or the AdreView™ administration procedure).

11.2 Clinical Data Management

A CRO will be responsible for the processing and quality control of the data. Data management will also be carried out by a CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

11.3 Archiving

All study documentation at the investigator site and Sponsor site will be archived in accordance with ICH E6- GCP, and the Sponsor/CRO's quality standards and SOPs.

Current EU Directive and ICH guidelines collectively require that essential clinical study documents (including eCRFs) other than the patient's medical files must be retained for the following time period:

- For at least 15 years after completion or discontinuation of the study,
- Or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region,
- Or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

National guidelines and regulations in individual countries should be followed as appropriate.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analysed by a Sponsor-designated CRO. Any data analysis carried out independently by the investigator should be submitted to the Sponsor before publication or presentation.

Data from participating centres in this protocol will be combined so that an adequate number of patients will be available for analysis. The data will be summarised with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software, Version 9.2 or higher. Descriptive statistics for continuous data in summary tables will include the number of patients in the analysis (n), mean, standard deviation (SD), median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. For the AdreView™ and SoC groups, the baseline value will be the last observation obtained before randomisation. All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual patient values. All summary tables and data listings will be separated by enrolment groups. The planning and reporting of statistical analysis will be carried out as described in the CRO's SOPs governing clinical studies.

12.2 Populations for Analysis

A patient is defined as having been included into the study if he/she has met all inclusion criteria, none of the exclusion criteria, and has been assigned to 1 of the enrolment groups (the AdreView™ group or the SoC group). The primary efficacy population is defined as those patients who were randomised to the AdreView™ group or the SoC group.

All randomised patients will be analysed for efficacy in the group to which they were randomised.

The safety population is defined as all patients who were enrolled in the study. All patients will be analysed for safety in the enrolment group to which they were assigned.

12.2.1 Determination of Safety and Efficacy Population

The rules for determination of the efficacy populations (primary and secondary) and the safety population are given in Section 12.2 above. Protocol violations will play no part in patient inclusion in the efficacy or safety populations.

12.3 Patient Demographics/Other Baseline Characteristics

A table will be provided with the following information:

- Number of patients screened/enrolled.
- Number of patients included in the efficacy analysis.
- Number of patients included in the safety analysis.
- Number of patients withdrawn from the study and the reason for withdrawal.

Demographic information (age, height, weight, and body mass index [BMI]) will be summarised using descriptive statistics. Gender and race will be summarised by counts and percentages.

Medical histories will be summarised by counts and percentages. Prior and concurrent medications will be recorded and coded using a standard classification system and grouped by primary and secondary classes, if applicable.

12.4 Study Treatments

For each AdreView™ administration, the dose (MBq) and volume (mL) will be summarised.

12.5 Primary Analysis

12.5.1 Variable

The primary endpoint is all-cause mortality

12.5.2 Statistical Hypothesis, Model, and Method of Analysis

This is an event-driven study. The primary efficacy analysis will take place after 247 instances of the primary efficacy endpoint have accrued. The primary efficacy endpoint will be analysed for non-inferiority. If the upper bound of the confidence interval is less than 1, superiority will be claimed/ established.

The primary null hypothesis is: H_0: hazard ratio (HR) (AdreView™ group / SoC) $\geq HR_0$.

The primary alternative hypothesis is: H_a: HR (AdreView™ group / SoC) $< HR_0$.

For this study, HR_0 is chosen to be 1.20.

The primary efficacy analysis will be performed in the primary efficacy population using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (SoC vs AdreView™ group) as the only covariate.

This analysis will be performed at a 1-sided alpha value of 0.025.

12.5.3 Handling of Missing Values/Censoring/Discontinuations

No imputation will be performed for any of the efficacy endpoints.

12.5.4 Supportive Analyses

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (AdreView™ group vs. SOC), LVEF, NYHA Classification, and BNP or NT proBNP as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

12.6 Secondary Analyses

If the primary efficacy analysis is statistically significant, the key secondary endpoints, as identified in Section 10.1.2, will be analysed in hierarchical order, according to their order in Section 10.1.2. If the analysis of the first key secondary endpoint is statistically significant, then the hierarchical analysis will continue with analysis of the second key secondary endpoint. However, if the analysis of the first key secondary endpoint is not statistically significant, then the hierarchical analysis will stop after analysis of the first key secondary endpoint. This method will continue until either all of the key secondary endpoints have been analysed hierarchically or the analysis of one of the key secondary endpoints is not statistically significant, at which point the hierarchical analysis of key secondary endpoints will stop.

The non-key secondary endpoints will be analysed inferentially, but not hierarchically.

12.6.1 Efficacy Endpoints and Analyses (Secondary)

Key Secondary Endpoints

- A composite of the proportion of patients with hospitalisation or death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) or complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). This endpoint will be analysed for superiority. These proportions will be compared between the patients with H/M ≥1.60 in the AdreView™ group and the patients with H/M ≥1.60 in the SoC group, using the Cochran-Mantel-Haenszel test stratified by enrolling centre, using a 2-sided alpha value of 0.050.

- Cardiac death. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority [NI], using an NI margin of 1.20).

- Rate of hospitalisation for cardiovascular cause. This rate will be compared between the AdreView™ and SoC groups using the Miettinen and Nurminen methodology [Miettinen and Nurminen 1985], (non-inferiority [NI], using an NI margin of 1.20).

- Rate of all-cause hospitalisation. This rate will be compared between the AdreView™ and SoC groups using the Miettinen and Nurminen methodology [Miettinen and Nurminen 1985], (NI, using an NI margin of 1.20).

- A composite of the occurrence of resuscitated life-threatening ventricular tachycardia, unstable ventricular tachy-arrhythmias, SCD and resuscitated cardiac arrest. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority, using an NI margin of 1.20).

Additional Secondary Endpoints

- Syncope. The occurrence of this event will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis (non-inferiority, using an NI margin of 1.20).

- Clinical and healthcare resource utilisation data collected in this study including ICD implantation, all hospitalisations, treatment of AEs, and AdreView™ administration will be used in an economic evaluation of study outcomes for relevant geographies. These clinical and healthcare resource utilisation data will be summarised in the primary efficacy population and compared between the AdreView™ and SoC groups. These data will be analyzed with a superiority analysis, using a 2-sided alpha value of 0.05. These data may also be used for future health economic analyses.

- A composite of the rate of hospitalisation and death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) and a composite of the rate of complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation). The occurrence of these events will be analysed in the primary efficacy population using a Cox proportional hazards model as was performed in the primary efficacy analysis between the AdreView group and the SoC group. These data will be analyzed with a superiority analysis, using a 2-sided alpha value of 0.05.

12.6.2 Exploratory Variables and Analyses

[redacted]

[redacted]

12.6.3 Safety Variables and Analyses

The safety variables to be analysed include all events occurring after informed consent, all AEs, including AdreView™-emergent AEs, SAEs, vital sign data, physical examination results, clinical laboratory test data, and electrocardiographic data. All safety analyses will be performed in the safety population.

All events occurring after informed consent and AEs will be summarised by MedDRA system organ class and preferred term (PT). An overall summary of AEs will be presented. AdreView™-emergent AEs will also be presented by causal relationship to study drug. Summaries of SAEs, AdreView™-emergent SAEs and other significant AEs will also be presented.

For vital signs, clinical laboratory tests, ECG data, and baseline values will be summarised with descriptive statistics (mean, SD, median, minimum, and maximum) for each enrolment group. For vital signs, post-enrolment changes from baseline and shift tables of all post-administration changes from baseline versus time will also be generated for each cohort. In addition, potentially clinically significant values will be summarised for vital sign parameters. Physical examination data will be presented by enrolment group and time point. All safety data will be listed by enrolment group and patient number.

Safety variables will also be transmitted regularly to the independent statistician of the DSMB for their regular safety assessment as per the DSMB charter,

12.6.3.1 Clinical Laboratory Evaluation

Clinical laboratory tests will be performed at only the screening/enrolment visit. Descriptive statistics will be displayed for the observed values and changes from baseline.

Summarisation will be by cohort. In addition, all clinical laboratory data will be listed by enrolment group and patient number.

12.6.3.2 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital-sign variable and each time point, the following safety endpoints will be summarised by counts and percentages.

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than a pre-specified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats per minute for heart rate, 10 breaths per minute for respiratory rate.
- The occurrence of post-administration values outside the normal limits (Table 3, Section 15.3). Shift tables based on the normal range will be prepared.

All summarisations will be by enrolment group. In addition, all clinical laboratory data will be listed by enrolment group and patient number.

12.6.3.3 Electrocardiograms

Electrocardiograms will be performed at only the Screening/Enrolment visit. Descriptive statistics will be displayed for the observed values and changes from baseline. All summarisations will be by enrolment group. In addition, all ECG data will be listed by enrolment group and patient number.

12.6.3.4 Physical Examination

The number and percentage of patients with changes in physical examination status from normal at baseline (complete physical examinations) to abnormal at each post-randomisation (allocation) time point (brief physical examinations) (and vice versa) will be presented by cohort.

In addition, all physical examination data will be listed by enrolment group and patient number.

12.6.3.5 Adverse Events

All AEs occurring after informed consent will be recorded on the eCRF.

An overall summary of AEs will be presented, including the numbers of patients with any events occurring after informed consent, any AEs, any SAEs, any AdreView™-emergent AEs/SAEs, any causally related AdreView™-emergent AEs/SAEs, any severe AEs, any AEs leading to discontinuation of study drug, and any AEs leading to discontinuation from the study.

The number and percentage of patients with 1 or more AEs occurring after informed consent and the number and percentage of patients with 1 or more AdreView™-emergent AEs will be summarised by cohort, using MedDRA PTs and System Organ Classes. A patient will be counted only once within a System Organ Class or PT even if the patient experienced more than 1 event within a specific System Organ Class or PT.

The number and percentage of patients with AEs will also be summarised by maximum severity of AE (mild, moderate, or severe).

The number and percentage of patients with AEs will also be summarised by relationship to study drug. The Events eCRF page asks the following question: “Was there a reasonable possibility that the study drug caused the event?” with responses of “1 Yes, causal relationship is a reasonable possibility” or “2 No, causal relationship is not a reasonable possibility.”

A summary of the number and percentage of patients with SAEs and AdreView™-emergent SAEs will also be presented by MedDRA System Organ Class and PT.

All AEs will be listed by enrolment group and patient number, and AdreView™-emergent AEs/SAEs will be flagged.

The Sponsor will also summarise other significant AEs, defined as laboratory abnormalities that qualify as such AEs (other than those meeting the definition for serious) and any events that led to an intervention (including premature discontinuation of AdreView™, dose reduction, or significant additional concomitant therapy), in addition to those reported as SAEs.

12.6.4 Resource Utilisation

Resource utilisation, including but not limited to ICD implantation, hospitalisation, treatment of AEs, and AdreView™ administration, will be analysed as detailed in Section 12.6.1.

12.7 Interim Analysis

The DSMB will perform a continuous monitoring of the safety of the study by regular analysis of safety data. This analysis will be done based on blinded data but the DSMB retains the right to request unblinding of the data after their safety review. The reasons for unblinding the data will be documented in the DSMB meeting minutes.

Additionally, during the course of the trial the DSMB may recommend to the ESC and Sponsor to perform the following interim analyses:

- An interim analysis for futility that will be conducted to verify the sample size assumptions and therefore the power of the study to achieve its objectives. Based on these results, DSMB may recommend to the ESC and Sponsor to re-calculate the sample size, prolong or terminate the study prematurely. The Sponsor will make the final decision. This interim analysis for futility will be performed using the methods of [Chen et al. 2004]. The CRO, using unblinded data, will estimate conditional power and perform sample size re-estimation. The CRO will then give these analysis results to the independent statistician on the DSMB. Since this analysis is unblinded, there will be a small adjustment to the study's final alpha value.

- An interim analysis for efficacy. In that case, it could be conducted using the method described by [O'Brien et al. 1979], the 1-sided alpha value for the interim analysis for efficacy would be 0.0027.

12.8 Sample Size Calculation

Assumptions:

The all-cause mortality rate that is expected in the study has been estimated using the all-cause mortality rate observed in Study GE-122-016 at 36 months (internal report). It is assumed:

	Patients with 25%≤LVEF≤30%		Patients with 30%≤LVEF≤35%	
	%	Mortality Rate	%	Mortality Rate
H/M ratio <1.6	79%	20.25%	75%	15.14%
H/M ratio ≥1.6	21%	9.72%	25%	4.68%

In addition, the following observations or assumptions were taken: the ratio of patients with 25%≤LVEF≤30% vs 30%≤LVEF≤35% is expected to be 1:4 to account for the prior enrollment of only patients with 30%≤LVEF≤35%; the hazard ratio of patients with ICD implantation vs with usual care in the existing practice is 0.9 [Køber et al. 2016]. Referring to existing practice, only 15% of patients with 25%≤LVEF≤35% currently receive ICD. Accordingly, the number of patients who currently do not receive ICD but who will receive it according to protocol and the number of patients who currently receive ICD and who will not receive it according to protocol have been calculated. In addition, the all-cause mortality rate of patients currently not receiving ICD but who will receive according to protocol (85% of patients with H/M ratio <1.6 in the AdreView™ group) has been corrected to take into account the 31% reduction in all-cause mortality observed at 20 months in the MADIT II trial [Moss et al. 2012]. These assumptions led to a composite mortality rate of 11.34% in the AdreView™ group and 13.33% in the SoC group. The sample size is estimated with the hypothesis of not having a relative increase of mortality rate in excess of 20% and with the following assumptions:

- Alpha = 0.025, 1-sided.
- Statistical power = 80%.
- 1:1 randomisation to AdreView™ and SoC groups.
- H_0: $HR \geq HR_0$ vs H_1: $HR < HR_0$. $HR_0 = 1.20$.
- Assumed HR: 0.84.
- Accrual time: 18 months.
- The total study duration: 48 months.
- AdreView™ group survival rate at 36 months: 0.887.

Based on the above assumptions, the required total number of events will be 247, and the required total number of randomized patients will be 2001.

The planned study accrual will be at least 2354 patients screened in order to randomize at least 2001 patients in the study.

12.9 Non-Inferiority Margin

The NI margin to be used for the analyses summarized in Sections 12.5.2 and 12.6.1 will be 1.20.

12.10 Power for Analysis of Critical Secondary Variables

Sample size estimates were also performed using plausible assumptions for the occurrence of the first key secondary endpoint, a composite of the proportion of patients with hospitalisation or death related to major complications of device implantation (i.e., need for thoracotomy, pericardiocentesis, or vascular surgery) or complications of long-term device therapy (i.e., infection not leading to hospitalisation, lead and/or generator removal/replacement, inappropriate shocks, explantation).

The following assumptions were made for these sample size estimates:

- Superiority analysis
- Alpha = 2-sided 0.05
- Power = 80% and 90%
- 1:1 randomisation to AdreView™ and SoC groups
- Proportion of SoC patients with H/M ≥1.60 who have composite endpoint of harm (summarized above) from ICD implantation = 5%, 6%, 7%, 8%, 9%, or 10%.
- Proportion of AdreView™ group patients with H/M≥1.60 who have composite endpoint of harm from ICD implantation = 0 (approximated by 0.0001).

Based on the above, the total sample size will range from 156 to 486 patients overall with a H/M ratio ≥1.6.

Thus, the sample size estimated for the primary efficacy endpoint is also adequate for the first key secondary endpoint (assuming 24% of patients in both the AdreView™ and SoC groups will have a H/M ratio ≥1.6, approximately 500 patients overall with a H/M ratio ≥1.6 is expected).

12.11 Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all patients in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.12 Rules for Excluding Patients from Analysis

All patients randomised will be included in the analyses unless otherwise specified.

12.13 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory, Institutional and Ethical Review

Before starting this study, the protocol (authorised by the Sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC/IRB. The study will not start before the IEC/IRB gives written approval or a favourable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorised) protocol will be initiated without the IEC's/IRB's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration. The Sponsor will authorise and the principal investigator(s) will sign the protocol amendment prior to submission to the IEC/IRB. Protocol amendments should be submitted to the IEC/IRB without delay.

13.2 Investigator's Responsibilities

13.2.1 Overall Responsibilities

The investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that cannot comply with these standards will be documented.

13.2.2 Patient Informed Consent

Written and oral information about the study in a language understandable by the patient will be given to all patients. Each patient's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the patient's medical record and the investigator will sign, date and time the informed consent form after the patient has signed, dated and recorded the time. The investigator(s) will keep the original consent forms and copies will be given to the patients.

13.2.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorised personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorised members of IECs/IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

13.2.4 Confidentiality Regarding Study Patients

The investigator(s) must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations) submitted to the Sponsor/CRO, patients will not be identified by their names, but by an identification code (e.g., study patient number).

Personal medical information may be scrutinised for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorised persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances.

13.4 Study Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

Study monitoring will be performed in accordance with ICH E6-GCP, the Sponsor/CRO SOPs, the protocol, and applicable local regulations.

As part of a concerted effort to fulfil these obligations, the Sponsor will authorise a CRO to perform monitoring tasks and visit the centre(s) during the study as well as maintain frequent telephone and written communication. The investigator will permit the CRO personnel to monitor the study as frequently as is deemed necessary and provide access to medical records

to ensure that data are being recorded adequately, that data are verifiable and that the protocol is adhered to.

13.5 Audit and Inspection

According to ICH E6-GCP, the Sponsor or regulatory authorities may audit the investigational site. The Sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.6 Insurance

This study is covered under the Sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study Sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.7 Publication Policy

Presentations, abstracts, posters, publications and any other scientific communications regarding the study protocol, conduct, and results will be managed by the ESC through a Publication Committee. The Publication Committee shall have the right to publish the results of their work conducted under this protocol, subject to providing the Sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission. Investigators shall comply with this policy.

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15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for this study is the IB. The reference document provides up-to-date information on the efficacy and safety of AdreView™, and is used for assessing expectedness of Serious Adverse Drug Reactions, in order to determine regulatory reportability. An unexpected adverse drug reaction is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable product information, e.g., the IB.

15.2 AdreView™ (Iobenguane I^{123} Injection)

AdreView™ must be ordered for each specific use date. It is recommended that this order be placed a minimum of 2 weekdays (Monday through Friday) before the scheduled visit date. Orders placed less than 2 weekdays before the scheduled visit must be approved by the Sponsor.

If AdreView™ is to be administered in the morning, the patient should abstain from eating or drinking (other than water) after midnight on the day of AdreView™ imaging. If AdreView™ is to be administered in the afternoon, the patient may have a light breakfast, after which the patient should abstain from eating or drinking (other than water). The patient should lie quietly for at least 15 minutes prior to administration of AdreView™. The first set of images will be obtained at 3 hours and 50 minutes post-injection and will be comprised of an anterior planar imaging of the chest performed according to the Imaging Manual provided by the Sponsor. This image will be followed by SPECT acquisition in accordance with said manual. While the planar imaging will be used for the primary and secondary efficacy analysis, the SPECT imaging will be used for exploratory analysis

For each imaging procedure, the patient will receive AdreView™ at rest, administered as an intravenous injection. The activity of AdreView™ should be measured in a dose calibrator within 1 hour prior to the scheduled administration time. The activity and time of measurement will be recorded on the eCRF. Aseptic conditions must be observed during handling of a patient dose. AdreView™ does not contain preservatives. The Sponsor or the designated CRO may request to review the quality control log book on the calibrators.

AdreView™ must be administered on the date for which the product is calibrated and no later than 6 hours post-calibration time. The preparation should be stored at 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F). Storage should take place in accordance with national regulations for radioactive material.

The administration of radiopharmaceuticals creates risks to other persons, from external radiation or contamination from spills of urine, vomiting, etc. Waste must be disposed of according to national regulations for radioactive material.

15.3 Normal Limits for Vital Signs and ECG Intervals

Table 3 Criteria for Normal Limits for Vital Signs

Vital Signs Parameter	Normal Limits	
	Low	High
Systolic BP (mmHg)	85	140
Diastolic BP (mmHg)	60	90
Heart Rate (bpm)	60	100
Respiratory Rate (rpm)	12	22
Oxygen Saturation (%)	90	100
Body Weight (kg)[a]	41	113
Body Mass Index (kg/m²)[b]	18.5	24.9

[a] Changes in body weight are evaluated by the investigator (without taking height into account) since BMI is not collected on the eCRF.

[b] BMI is calculated and analysed retrospectively by the Sponsor, at which time height is taken into account.

Table 4 Criteria for Normal Limits for ECGs

ECG Variable	Normal Limits (ms)	
	Low	High
PR interval	120	200
QRS interval	50	120
RR interval	600	1000
QT interval (gender not specified)	-	≤440
QTc interval[a] (gender not specified)	-	≤440

[a] No lower boundary set for QTc.

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

Reasons for Amendment

- Inclusion criterion (6) is revised to allow LVEF assessment performed within 3 months before or at time of enrolment to be used. This change increases the flexibility of investigators to recruit patients without having an impact on patient safety, scientific validity of the trial, or quality of the data. The amended criterion continues to adhere to international heart failure (HF) guidelines and additional wording stipulating a 40-day time lapse between hospitalisation for HF or acute coronary syndrome ensures that inclusion criterion number (7) remains applicable in case the LVEF determination is made before the time of enrolment.

- A blood sample for NT-proBNP is added as an alternative to BNP.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

Description of Changes

Section 6.1, Study Design and Plan, Paragraph 8

Previously read:

At the screening/enrolment visit, LVEF function determination will be performed. Only patients with 30%≤LVEF≤35% will be considered for inclusion. Patients with LVEF >35% will be excluded. Study procedures will be performed as detailed in Section 9.

Now reads:

Only patients with 30%≤LVEF≤35% will be considered for inclusion. Patients with LVEF >35% will be excluded. *Patients must have 30%≤LVEF≤35% as measured in the previous 3 months before enrolment with no hospitalisations for HF or acute coronary syndrome during this period of time. In case these patients have a hospitalisation for HF or acute coronary syndrome, the LVEF measurement will only be valid if performed 40 days after this event. Patients without a LVEF measurement will have the test performed at screening. All LVEF images will be sent to the Sponsor.* Study procedures will be performed as detailed in Section 9.

Section 7.2, Inclusion Criteria, Inclusion Criterion (6)

Previously read:

30%≤LVEF≤35%, performed at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted].

Now reads:

30%≤LVEF≤35%, performed *within 3 months before or* at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted].
In case LVEF measurement is performed within 3 months before enrolment, measurement should be performed at least 40 days after a hospitalisation for HF or acute coronary syndrome (including myocardial infarction), and to be valid, method of measurement should be in accordance with the protocol and the imaging exam should be made available to the Sponsor in digital format.
In case several valid LVEF measurements are available, the closest to enrolment will be used for inclusion determination.

Section 9, Study Procedures, Table 1 (Study Schedule of Events)

Previously read:

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographic Information	X						
Medical/Surgical History	X			X	X		X
Concomitant Medications [b]	X			X	X		X
Pregnancy Test [c]	X					X	
Pre-Inclusion Events	X						
Physical examination (complete)	X						
Brief Physical examination				X	X		X
Blood samples for clinical laboratory evaluation	X						
Vital signs [d]	X			X	X		X
ECG	X						
LVEF assessment (radionuclide or contrast ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D 2D echocardiography (Simpson's or multidisc method or equivalent only)) [e]	X						
Assignment to study group		X					
AdreView™ Administration [f]			X			X	
Injection site monitoring			X			X	
Image Acquisition (Planar and SPECT) [e, g]			X			X	
ICD Implantation (if applicable) [h]			X				
ICD interrogation (if applicable)				X	X		X

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]
AEs, SAEs and AdreView™-emergent AEs[i]	X	X	X	X	X	X	X
Data collection pertaining to primary and secondary endpoints			X	X	X	X	X

*All procedures listed do not necessarily need to be performed during a single day

a Signed and dated informed consent must be obtained before eligibility assessments, including pregnancy test, are commenced.

b Recorded up to 30 days before screening.

c A serum or urine pregnancy test will be performed for all women of childbearing potential.

d Before vital signs are measured, the patient should be resting for at least 5 minutes. The same arm and position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contra-lateral to the site of AdreView™ administration whenever possible.

e Image files will be sent to the Sponsor.

f AdreView™ will be administered to all patients. First AdreView™ administration should be performed in the 15 (+7) days post-randomisation. For the low-risk cohort only, a second AdreView™ administration should be administered at 2 years (±30 days) post-randomisation, unless patient withdraws prior to study termination or has already received an ICD. In this case the second AdreView™ scan will be offered before withdrawal becomes effective. Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

g At 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of planar images, and whenever possible followed by SPECT acquisition, according to the imaging manual. Patients with LVEF 30% to 35% with an H/M ratio ≥1.6 will have a second AdreView™ scan at 2 years (±30 days) post-randomisation.

h Patients in the randomised AdreView™ group who are assessed as high risk, and patients in the SoC group according to the standard of care in each investigational site derived from the local implementation of internationally accepted HF guidelines. ICD implantation should be performed according to clinical practice and should be performed within 45 days after randomisation.

i AdreView™-emergent AEs are defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

j Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

Now reads:

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographic Information	X						
Medical/Surgical History	X			X	X		X
Concomitant Medications [b]	X			X	X		X
Pregnancy Test [c]	X					X	
Pre-Inclusion Events	X						
Physical examination (complete)	X						
Brief Physical examination				X	X		X
Blood samples for clinical laboratory evaluation	X						
Vital signs [d]	X			X	X		X
ECG	X						
Check LVEF values within the previous 3 months or perform LVEF assessment. [e]	X						
Assignment to study group		X					
AdreView™ Administration [f]			X			X	
Injection site monitoring			X			X	
Image Acquisition (Planar and SPECT) [e, g]			X			X	
ICD Implantation (if applicable) [h]			X				
ICD interrogation (if applicable)				X	X		X
AEs, SAEs and AdreView™-emergent AEs[i]	X	X	X	X	X	X	X
Data collection pertaining to primary and secondary endpoints			X	X	X	X	X

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]

*All procedures listed do not necessarily need to be performed during a single day

a Signed and dated informed consent must be obtained before eligibility assessments, including pregnancy test, are commenced.

b Recorded up to 30 days before screening.

c A serum or urine pregnancy test will be performed for all women of childbearing potential.

d Before vital signs are measured, the patient should be resting for at least 5 minutes. The same arm and position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contra-lateral to the site of AdreView™ administration whenever possible.

e *Acceptable methods of LVEF assessment are radionuclide or contrast ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D 2D echocardiography (Simpson's or multidisc method or equivalent only).* Image files will be sent to the Sponsor.

f AdreView™ will be administered to all patients. First AdreView™ administration should be performed in the 15 (+7) days post-randomisation. For the low-risk cohort only, a second AdreView™ administration should be administered at 2 years (±30 days) post-randomisation, unless patient withdraws prior to study termination or has already received an ICD. In this case the second AdreView™ scan will be offered before withdrawal becomes effective. Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

g At 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of planar images, and whenever possible followed by SPECT acquisition, according to the imaging manual. Patients with LVEF 30% to 35% with an H/M ratio ≥1.6 will have a second AdreView™ scan at 2 years (±30 days) post-randomisation.

h Patients in the randomised AdreView™ group who are assessed as high risk, and patients in the SoC group according to the standard of care in each investigational site derived from the local implementation of internationally accepted HF guidelines. ICD implantation should be performed according to clinical practice and should be performed within 45 days after randomisation.

i AdreView™-emergent AEs are defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

j Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

Section 9.1, Screening / Enrolment Visit, Paragraph 3

Previously read:

At the screening visit, LVEF function determination will be performed. Acceptable methods for LVEF determination are as follows: radionuclide ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D or 2D echocardiography (Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted).

Now reads:

At the screening visit, LVEF function determination will be performed *in cases where a previous LVEF measurement is not available. If there is a previous LVEF measurement performed within 3 months of enrolment, the investigator will check that this measurement was performed when the patient had no hospitalisations for HF or acute coronary syndrome, or if such hospitalisation happened then the LVEF measurement was performed 40 days after the event.* Acceptable methods for LVEF determination are as follows: radionuclide ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D or 2D echocardiography (Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted). *LVEF images will be sent to the sponsor in electronic format.*

Section 9.1, Screening / Enrolment Visit, Bullet Point 5

Previously read:

Blood samples for serum chemistry and haematology and BNP determination will be collected (according to Table 2)

Now reads:

Blood samples for serum chemistry and haematology and BNP *or N-terminal pro b-type natriuretic peptide (NT proBNP)* determination will be collected (according to Table 2)

Section 10.2.1, Clinical Laboratory Evaluation, Table 2 (Clinical Laboratory Parameters)

Previously read:

Table 2 Clinical Laboratory Parameters

Serum Biochemistry	Haematology
Chloride	Haematocrit
Urea nitrogen	Haemoglobin
Creatinine	Platelet count
Bicarbonate	White blood cell (WBC) count
Sodium	Lymphocyte %
Potassium	
Glucose	Troponin
Alkaline phosphatase	ST2 and Gal 3 biomarkers (if available for on-site determination).
Aspartate transaminase	
Alanine transaminase	
Bilirubin (Total)	
Brain natriuretic peptide (BNP)	

Now reads:

Table 2 Clinical Laboratory Parameters

Serum Biochemistry	Haematology
Chloride	Haematocrit
Urea nitrogen	Haemoglobin
Creatinine	Platelet count
Bicarbonate	White blood cell (WBC) count
Sodium	Lymphocyte %
Potassium	
Glucose	Troponin
Alkaline phosphatase	ST2 and Gal 3 biomarkers (if available for on-site determination).
Aspartate transaminase	
Alanine transaminase	
Bilirubin (Total)	
Brain natriuretic peptide (BNP) *or N-terminal pro b-type natriuretic peptide (NT proBNP)*	

Section 12.5.4, Supportive Analyses

Previously read:

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (SoC vs AdreView™ group), LVEF, NYHA Classification, and BNP as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

Now reads:

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (SoC vs AdreView™ group), LVEF, NYHA Classification, and BNP *or NT proBNP* as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

16.2 Amendment A02

Reasons for Amendment

- The LVEF window is revised from 30%≤LVEF≤35% to 25%≤LVEF≤35%.
  As part of their remit, the SC continuously evaluates scientific data to ensure that trial integrity is aligned with up to date scientific evidence. Recent scientific evidence indicates that the benefits of additional risk stratification in patients with HF and reduced ejection fraction with LVEF of 30 to 35% may be also applicable to patients with lower LVEF values. Therefore, modification of the LVEF window from 30%≤LVEF≤35% to 25%≤LVEF≤35% is recommended by the SC. The DSMB has endorsed this change. The ESC discussed this amendment with the DSMB who noted that extending the study recruitment to LVEF values of 25 to 30% would still recruit patients for whom good stratification was possible. The introduction and rationale have been updated to support this.

- The sample size is recalculated based on modification of the LVEF entry criteria. Minor clarifications to the primary and secondary efficacy analysis are included.

- Investigators are reminded that patients with HF are considered potential candidates for ICD implantation for primary prevention of SCD only after they have been under guideline-directed medical therapy for at least 3 months.

- Investigators are reminded that should any patients not be receiving guideline-directed optimal medical therapy 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™ has been included to accommodate use in sites where there are logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.

- Clarification has been added about remote ICD interrogation to accommodate current clinical practice.

- A pregnancy test is added post-randomization, to be performed on the day of and prior to AdreView™ administration.

- The email address for the Global Pharmacovigilance mailbox is updated.
- The study time frame is updated.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

Description of Changes

Title of Study

Previously read:

AdreView™ Myocardial Imaging for Risk Evaluation – A multicentre trial to guide ICD implantation in NYHA class II & III heart failure patients with 30%≤LVEF≤35%. ADMIRE-ICD

Now reads:

AdreView™ Myocardial Imaging for Risk Evaluation – A multicentre trial to guide ICD implantation in NYHA class II & III heart failure patients with *25%*≤LVEF≤35%. ADMIRE-ICD

Section 4, Background Information and Study Rationale, Paragraphs 3 through 11

Previously read:

Current USA and European Union (EU) guidelines recommend implantation of an implantable cardioverter defibrillator device (ICD) in patients with left ventricular ejection fraction (LVEF) ≤35% to reduce the risk of sudden death. However, only about half of all patients who meet the guideline-derived criteria actually have a device implanted. Furthermore, during the first year of implantation, as few as 5% of patients who have a device implanted will actually experience an appropriate shock or pace termination of a fatal arrhythmia [Moss et al. 2012]. Thus, the majority of patients who do have a device implanted do not actually benefit from the device. These patients are not immune from the complications of device implantation and on-going care, including mechanical and infectious complications of the procedure itself, inappropriate device activation, device failure, and ultimately need for device replacement every several years. Despite optimal therapy and device care, approximately 2% of patients with devices will die suddenly each year, and 3% will die from other cardiac causes, usually HF or myocardial infarction. Furthermore, inappropriate shocks appear to be associated with a higher incidence of all cause and cardiovascular death [Moss et al. 2012]. Ideally only patients who will be saved will have a device implanted, and those who will not be saved will not have a device implanted. However, it is unlikely that this degree of risk stratification will be achieved as a patient's condition changes and their risk ranking will undoubtedly change with

it. Even with a device, annually 2% of patients will die of clinically adjudicated sudden death, although it is uncertain if this is an arrhythmic death.

Currently, the criterion widely used and accepted as a risk stratification tool for implantation of an ICD is a reduced LVEF, e.g., below 30% or 35% depending on countries practice. This is based on multiple large-scale studies having demonstrated a benefit in terms of patient's survival. However, several publications have demonstrated that within the patients with an impaired LVEF, a low-risk group (and even a high-risk group) can be identified who may not benefit from an ICD implantation [Goldenberg et al. 2008] [Buxton et al. 2007]. For instance, in a post-hoc analysis of the Multicentre Automatic Defibrillator Implant Trial II (MADIT II) study, this low-risk group (having none of the clinical risk factors as defined by the Authors), that represented nearly one third of the population included, had a 2-year mortality of 8% and not any benefit of ICD implantation was identified. Moreover, in the very high-risk group, no benefit was identified either [Goldenberg et al. 2008]. In the same study (MADIT II) it was also noted that only 35% of patients received appropriate shocks during a 3-year follow up [Chen and Zhou 2013].

More recently, the defined LVEF limits used in the MADIT I & II, DEFINITE, MUSTT and SCD-HeFT studies have been questioned. [Al-Khatib et al. 2014] have suggested that perhaps devices for primary prevention of SCD should only be implanted in patients with LVEF <30%, identifying a population of patients with LVEF between 30% and 35% that might not benefit of ICD implantation.

Therefore, using a cut-off point of LVEF <35% may not be the most accurate criterion for identifying patients at high risk of death and guiding ICD implantation.

Finally, ICD implant and care is expensive. In 2006, costs per implant per patient in the USA were estimated at USA$28,500-55,200 and annual follow up from USA$4,800-17,000 [Groeneveld et al. 2006]. A more recent study in the Netherlands found a life time costs for an ICD to range from €60,800-64,200 [Thijssen et al. 2014].

To improve risk-stratification of patients, new tools are required. Meta-iodobenzylguanidine (mIBG) is an analogue of norepinephrine that is taken up into cardiac sympathetic nerve endings in the same manner as NE. In HF this uptake is decreased and norepinephrine stores in the myocardium are depleted. This process can be imaged in situ by using scintigraphy with ^{123}I-mIBG which strongly correlates with established markers of HF severity. Findings on mIBG imaging are associated with poor outcomes, including risk of death or of requiring transplantation, and sudden death. In a study that included 81 HF patients with LVEF<35%, assessed by cardiac mIBG imaging at enrolment and followed-up for at least 5 years, [Kawai et al. 2015] demonstrated that the positive predictive value of mIBG score for identifying patients without SCD was 100% and therefore could be suitable to identify patients with HF who are at low risk for SCD and do not require an ICD. The ADMIRE-HF study examined the predictive value of AdreView™ (Iobenguane I^{123} injection) imaging in 961 patients with New York Heart Association (NYHA) functional class II or III HF and LVEF ≤35 percent [Jacobson et al. 2010]. It evaluated the heart/mediastinum (H/M) ratio at 4 hours after tracer injection as a risk factor for HF progression, arrhythmic event (sustained ventricular tachycardia, cardiac arrest, or appropriate ICD discharge), or cardiac death. The H/M ratio of radioactivity uptake was a

predictor for each of the individual event categories. An H/M ratio of <1.6 remained independently associated with cardiac events after adjustment for LVEF, b-type natriuretic peptide (BNP), and NYHA functional class.

In 2013, the Food and Drug Administration (FDA) approved GE Healthcare's AdreView™ (Iobenguane I^{123} injection) for the scintigraphic assessment of myocardial sympathetic innervation by measurement of the H/M ratio to assist in the evaluation of patients with NYHA class II or class III HF and left LVEF ≤ 35%. The label states that AdreView™ may be used to help identify patients with lower 1- and 2-year mortality risks, as indicated by an H/M ratio ≥1.6. The product information also highlights the limitations that AdreView™ utility has not been established for selecting a therapeutic intervention or for monitoring the response to therapy, nor for using the H/M ratio to identify a patient with a high risk for death.

All these findings have not yet been replicated prospectively, but represent a potentially powerful tool for reclassifying risk amongst patients previously thought to require device implantation. Particularly, HF patients having a LVEF between 30% and 35% for whom the benefit of ICD implantation seems uncertain would benefit the most of an adequate staging of their cardiovascular risk and guidance of ICD implantation.

Now reads:

Present USA and European Union (EU) guidelines recommend implantation of an implantable cardioverter defibrillator device (ICD) in patients with left ventricular ejection fraction (LVEF) ≤35% to reduce the risk of sudden death. *Canadian guidelines [Bennett et al. 2017] further specify that additional risk assessment be performed in patients with LVEF values of 30% to 35% due to a lack of data supporting the use of prophylactic ICDs in this population. Moreover, the recently-reported DANISH study has questioned the utility of prophylactic ICD therapy in patients with non-ischemic left ventricular dysfunction, possibly due to the lower risk of arrhythmic death with contemporary medical therapy. Further,* only about half of all patients who meet the guideline-derived criteria actually have *an ICD* implanted *reflecting the uncertainly of ICD benefit in patients with lesser degrees of left ventricular dysfunction. For example, in* the first year *after ICD* implantation, as few as 5% of patients will actually experience a *potentially fatal arrhythmia for which an ICD therapy is necessary* [Moss et al. 2012]. Thus, the majority of patients who have *an ICD* implanted *do not receive a survival benefit from it*. These patients are not immune from the complications of device implantation and on-going care, including mechanical and infectious complications of the procedure, inappropriate device activation, device failure, and ultimately need for device replacement. Despite optimal therapy and device care, approximately 2% of patients with devices will die suddenly each year, and 3% will die from other cardiac causes, usually HF or myocardial infarction. *Moreover,* inappropriate shocks *are* associated with a higher incidence of all cause and cardiovascular death [Moss et al. 2012]. Ideally, only patients who *will suffer a serious arrhythmia would have an ICD* implanted. *Yet,* it is unlikely that this degree of risk stratification *is attainable, given temporal changes in their underlying heart disease.*

Presently, the criterion widely used and accepted as a risk stratification tool for implantation of an ICD is a reduced LVEF, e.g., below 30% or 35% depending on *local guidelines*. This is based on multiple large-scale studies having demonstrated a benefit in terms of patient's

survival. However, several publications have demonstrated that within the patients with an impaired LVEF, a low-risk group (and even a high-risk group) can be identified who may not benefit from an ICD implantation [Goldenberg et al. 2008] [Buxton et al. 2007]. For instance, in a post-hoc analysis of the Multicentre Automatic Defibrillator Implant Trial II (MADIT II) study, this low-risk group (having none of the clinical risk factors as defined by the Authors), that represented nearly one third of the population included, had a 2-year mortality of 8% and not any benefit of ICD implantation was identified. Moreover, in the very high-risk group, no benefit was identified either [Goldenberg et al. 2008]. In the same study (MADIT II) it was also noted that only 35% of patients received appropriate shocks during a 3-year follow up [Chen and Zhou 2013].

More recently, the defined LVEF limits used in the MADIT I & II, DEFINITE, MUSTT and SCD-HeFT studies *(upper LVEF limit ≤30 or ≤35%)* have been questioned. [Al-Khatib et al. 2014] have suggested that perhaps devices for primary prevention of SCD should only be implanted in patients with LVEF <30%, identifying a population of patients with LVEF between 30% and 35% that might not benefit of ICD implantation, *which implies that LVEF alone is not sufficient to select those who would benefit from this therapy. More recent scientific evidence suggests that there are groups of patients that can benefit from additional risk stratification beyond an LVEF cut-off point. Results of a multicentre, randomised trial in 1112 patients with non-ischemic heart failure (median LVEF 25%; mean follow up of 67.2 months) showed that prophylactic ICD implantation was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care [Køber et al. 2016]. A pooled analysis of 6 randomised controlled trials (RCTs) encompassing 2970 patients with non-ischemic HF (upper LVEF limit ≤30 or ≤35%) concluded that while there is a role for ICDs in this population, "improvement in risk prediction models can help overcome the traditional reliance on ejection fraction for risk stratification of sudden cardiac death in these patients" [Golwala et al. 2016]. Another pooled analysis of the results of SCD-HeFT, MADIT-II and DEFINITE (all with LVEF ≤35%), assessing the benefit of the ICD, in comparison with optimal medical therapy alone in NHYA class III patients (n=1054) showed no significant survival benefit [Barra et al. 2016]. Risk stratification could also be improved in class II HF patients. Per the revised ESC guidelines, an ICD will prevent about 2 deaths per year for every 100 devices in patients with mild HF (NYHA class II) [Ponikowski et al. 2016].*

Therefore, using *any LVEF cut-off point alone to identify patients at high risk of death and guide ICD implantation lacks the necessary accuracy. Additional biomarker tests may provide the necessary information to identify those patients who will benefit from an ICD.*

Finally, ICD implant and care is expensive. In 2006, costs per implant per patient in the USA were estimated at USA$ 28,500-55,200 and annual follow up from USA$ 4,800-17,000 [Groeneveld et al. 2006]. A more recent study in the Netherlands found a life time costs for an ICD to range from € 60,800 to € 64,200 [Thijssen et al. 2014].

New tools are required to improve risk-stratification. Meta-iodobenzylguanidine (mIBG) is an analogue of norepinephrine that is taken up into cardiac sympathetic nerve endings in the same manner as NE. In HF this uptake is decreased and norepinephrine stores in the myocardium are depleted. This process can be imaged in situ by using scintigraphy with ^{123}I-mIBG which strongly correlates with established markers of HF severity. Findings on mIBG imaging are

associated with poor outcomes, including risk of death or of requiring transplantation, and sudden death. In a study that included 81 HF patients with LVEF <35%, assessed by cardiac mIBG imaging at enrolment and followed-up for at least 5 years, [Kawai et al. 2015] demonstrated that the positive predictive value of mIBG score for identifying patients without SCD was 100% and therefore could be suitable to identify patients with HF who are at low risk for SCD and do not require an ICD. The ADMIRE-HF study examined the predictive value of AdreView™ (Iobenguane I^{123} injection) imaging in 961 patients with New York Heart Association (NYHA) functional class II or III HF and LVEF ≤35% [Jacobson et al. 2010]. It evaluated the heart/mediastinum (H/M) ratio at 4 hours after tracer injection as a risk factor for HF progression, arrhythmic event (sustained ventricular tachycardia, cardiac arrest, or appropriate ICD discharge), or cardiac death. The H/M ratio of radioactivity uptake was a predictor for each of the individual event categories. An H/M ratio of <1.6 remained independently associated with cardiac events after adjustment for LVEF, b-type natriuretic peptide (BNP), and NYHA functional class. *Based on these data, a recent decision-analytical model was developed to estimate the potential outcomes of using ^{123}I-mIBG to screen HF eligible for an ICD [O'Day et al. 2016]. Results of the analysis showed that ^{123}I-mIBG imaging could lead to a reduction of ICD utilization particularly in the 25-35% LVEF group. Below an LVEF value of 25%, the low number of patients expected to be at low risk based on the H/M ratio would indicate that it is not advisable to use this strategy in those with LVEF <25%.*

In 2013, the Food and Drug Administration (FDA) approved GE Healthcare's AdreView™ (Iobenguane I^{123} injection) for the scintigraphic assessment of myocardial sympathetic innervation by measurement of the H/M ratio to assist in the evaluation of patients with NYHA class II or class III HF and left LVEF ≤35%. The label states that AdreView™ may be used to help identify patients with lower 1- and 2-year mortality risks, as indicated by an H/M ratio ≥1.6. The product information also highlights the limitations that AdreView™ utility has not been established for selecting a therapeutic intervention or for monitoring the response to therapy, nor for using the H/M ratio to identify a patient with a high risk for death.

All these findings have not yet been replicated prospectively, but represent a potentially powerful tool for reclassifying risk amongst patients previously thought to require device implantation. *In particular, NYHA Classes II and III* HF patients having a LVEF between 25% and 35% for whom the benefit of ICD implantation seems uncertain would benefit the most *from* an adequate staging of their cardiovascular risk and guidance of ICD implantation.

Section 5, Study Objectives and Purpose, Primary Objective

Previously read:

To demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation in a population of NYHA class II and III HF patients with 30%≤LVEF≤35%. This will be achieved by comparing all-cause mortality observed in the AdreView™ -guided therapy group to that observed in patients receiving the 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.

Now reads:

To demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation in a population of NYHA class II and III HF patients with *25*%≤LVEF≤35%. This will be achieved by comparing all-cause mortality observed in the AdreView™ -guided therapy group to that observed in patients receiving the 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.

Section 6.1, Overall Study Design and Plan, First Paragraph

Previously read:

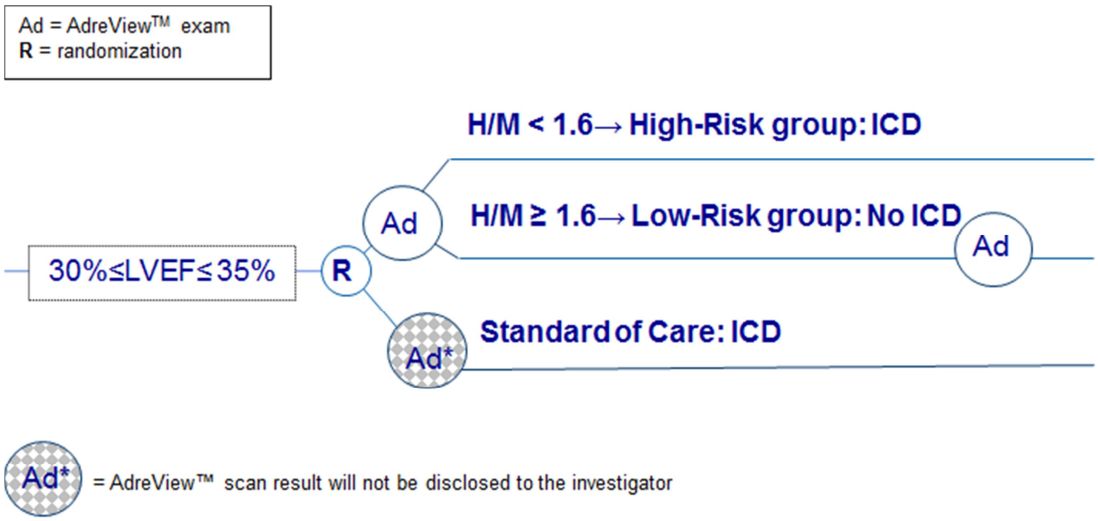
This is an event-driven Phase IIIb, multicentre, randomised, clinical study to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation, in NYHA class II and III HF patients with 30%≤LVEF≤35%, and in particular, for identifying patients who are at low risk for SCD and who would not benefit, or may suffer harm, from implantation of an ICD device.

Now reads:

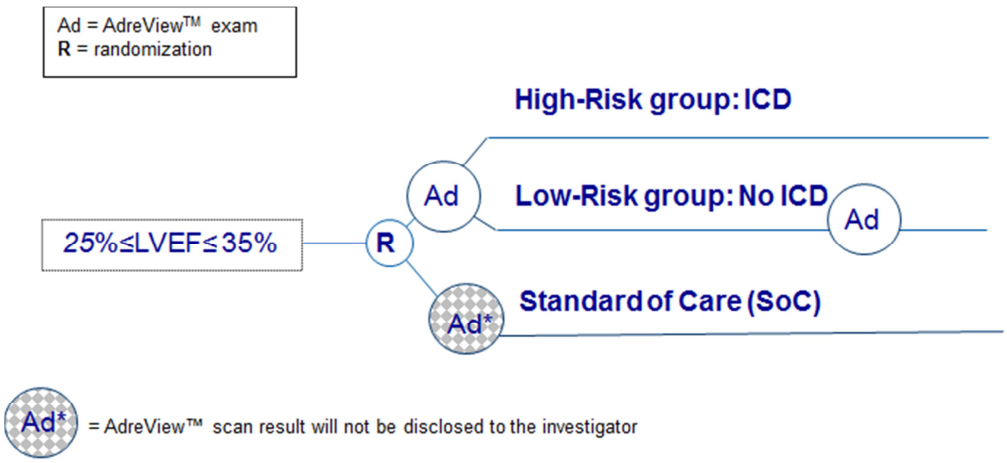
This is an event-driven Phase IIIb, multicentre, randomised, clinical study to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of ICD implantation, in NYHA class II and III HF patients with *25*%≤LVEF≤35%, and in particular, for identifying patients who are at low risk for SCD and who would not benefit, or may suffer harm, from implantation of an ICD device.

Section 6.1, Overall Study Design and Plan, Figure 1

Previously read:



Now reads:



Section 6.1, Overall Study Design and Plan, Paragraphs 6 through 9

Previously read:

This study will be conducted at approximately 130 centres in the USA, Canada and Europe. At least 2,607 patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least 2216 patients.

It is anticipated that patients will participate in the study until sufficient endpoints have been accrued which may correspond to an average of 2.75 to 3 years individual follow-up. The total study duration is expected to be approximately 4 years and the total required number of primary endpoint events observed is 247.

Only patients with 30%≤LVEF≤35% will be considered for inclusion. Patients with LVEF >35% will be excluded. Patients must have 30%≤LVEF≤35% as measured in the previous 3 months before enrolment with no hospitalisations for HF or acute coronary syndrome during this period of time. In case these patients have a hospitalisation for HF or acute coronary syndrome, the LVEF measurement will only be valid if performed 40 days after this event. Patients without a LVEF measurement will have the test performed at screening. All LVEF images will be sent to the Sponsor. Study procedures will be performed as detailed in Section 9.

Patients with 30%≤LVEF≤35%, and meeting all other inclusion criteria and not meeting any of the exclusion criteria, will be randomly assigned to the AdreView™ group or the SoC group. All patients will be scheduled for an AdreView™ scan. The results of the AdreView™ scan in the SoC group will remain blinded to the investigator to avoid any influence in the decision of implanting an ICD. The results of the AdreView™ scan in the AdreView™ group will be known to the investigator and as such be used to assess their cardiovascular risk level and determine ICD implantation. Patients with AdreView™ H/M ratio <1.6 (high 1- and 2-year mortality risk) will undergo ICD device implantation. Patients with AdreView™ H/M ratio ≥1.6 (low 1- and 2-year mortality risk) will receive guideline-directed medical therapy according to clinical standard practice medical therapy and will not undergo ICD implantation. Patients in this later group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. Patients allocated to the SoC group will undergo ICD implantation and will be managed and followed up in accordance with internationally accepted HF guidelines.

Now reads:

This study will be conducted at approximately 130 centres in the USA, Canada and Europe. At least *2354* patients will be screened (taking into account approximately 15% screen failure rate) in order to include at least *2001* patients.

It is anticipated that patients will participate in the study until sufficient endpoints have been accrued which may correspond to an average of 2.75 to 3 years individual follow-up. The total study duration is expected to be approximately *6* years and the total required number of primary endpoint events observed is 247.

Only patients with *stable heart failure who have been under guideline-directed optimal medical therapy for at least 3 months and have 25*%≤LVEF≤35% will be considered for inclusion. Patients with LVEF >35% will be excluded. Patients must have *25*%≤LVEF≤35% as measured in the previous 3 months before enrolment with no hospitalisations for HF or acute coronary syndrome during this period of time. In case these patients have a hospitalisation for HF or acute coronary syndrome, the LVEF measurement will only be valid if performed 40 days after this event. Patients without a LVEF measurement will have the test

performed at screening. All LVEF images will be sent to the Sponsor. Study procedures will be performed as detailed in Section 9.

Patients with *25*%≤LVEF≤35%, and meeting all other inclusion criteria and not meeting any of the exclusion criteria, will be randomly assigned to the AdreView™ group or the SoC group. All patients will be scheduled for an AdreView™ scan. The results of the AdreView™ scan in the SoC group will remain blinded to the investigator to avoid any influence in the decision of implanting an ICD. The results of the AdreView™ scan in the AdreView™ group will be known to the investigator and as such be used to assess their cardiovascular risk level and determine ICD implantation. Patients with AdreView™ H/M ratio <1.6 (high 1- and 2-year mortality risk) will undergo ICD device implantation. Patients with AdreView™ H/M ratio ≥1.6 (low 1- and 2-year mortality risk) will *continue to* receive guideline-directed *optimal* medical therapy according to clinical standard practice medical therapy and will not undergo ICD implantation. Patients in this later group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. Patients allocated to the SoC group will undergo ICD implantation and will be managed and followed up in accordance with internationally accepted HF guidelines.

Section 6.3, Study Timeframe

Previously read:

Patient recruitment is planned to start in 4Q 2015. The duration of this study will be dependent on the time taken to achieve a total of 247 primary endpoint events in the study. The expected duration is 4 years (including an 18-month recruitment period and mean observational time per patient of 2.75 to 3 years).

Now reads:

Patient recruitment is planned to start in 4Q 2015. The duration of this study will be dependent on the time taken to achieve a total of 247 primary endpoint events in the study. The expected duration *of the study is 6* years (*assuming a 32*-month recruitment period and mean observational time per patient of 2.75 to 3 years).

Section 6.4, Risks and Benefits to Patients, Paragraphs 1 through 4

Previously read:

The study rationale and justification have been detailed in Section 4 above.

Current HF guidelines recommend implantation of ICD for primary prevention of SCD to reduce total mortality in NYHA class II and III patients with a LVEF≤35% [Yancy et al. 2013]. However, there are still doubts about the survival benefit of this treatment in certain categories of patients. Recently [Al-Khatib et al. 2014] have suggested that perhaps devices for primary

prevention of SCD should only be implanted in patients with LVEF<30%, thus identifying a population of patients with 30%≤LVEF ≤35% that might not benefit from ICD implantation. It is expected that better risk stratification will lead to better patient selection improving the risk/benefit of ICD implantation.

The study will recruit HF patients with 30%≤LVEF ≤35%. Patients will be randomised to one of the 2 following groups. In one group, AdreView™ imaging will lead the decision of whether or not to implant an ICD and in the other it will not (the AdreView™ scan result will not be disclosed to the investigator). AdreView™ is a diagnostic radiopharmaceutical approved in the USA and several European countries for the identification of HF patients, NYHA class II and III with lower 1- and 2-year mortality risk. Patients randomised to the AdreView™ arm will have an ICD implanted within 45 days of randomisation if they are deemed to be at high risk according to the definition in Section 6.1 (AdreView™ H/M ratio [measured on an anterior planar image obtained at 3 hours and 50 minutes post-injection and calculated according to the instructions in the Imaging Manual] lower than 1.6). These patients should then face the same risks and benefits as those managed according to guidelines in the regular clinical setting.

Patients considered to be at low risk by AdreView™ imaging (i.e., those with a planar image H/M ratio≥1.6) will not receive an ICD, thus avoiding the exposure to complications; however they may face the risk that a potentially beneficial ICD implantation is withheld. GE Healthcare-sponsored study reports used for regulatory submissions (MBG311, MBG312 and MBG313; reports available upon request) have consistently showed a significant difference in all-cause and cardiac mortality between the high and the low risk groups in favour of the latter. These patients will also receive the usual guideline-directed medical therapy needed for their condition, including all the necessary follow-up visits and tests deemed necessary by the physician in charge. In addition, these patients will undergo a second AdreView™ H/M ratio determination 2 years after the first one in order to assess if their risk level has increased and ICD implantation is warranted. Moreover and as described in the protocol, the DSMB will regularly assess all safety aspects of the study.

Now reads:

The study rationale and justification have been detailed in Section 4 above.

Current HF guidelines recommend implantation of ICD for primary prevention of SCD to reduce total mortality in NYHA class II and III patients with a LVEF≤35% *after a minimum of 3 months of guideline-directed optimal medical therapy* [Yancy et al. 2013]. However, there are still doubts about *using the LVEF as the main criteria to decide on ICD implantation*. [Al-Khatib et al. 2014] have suggested that perhaps devices for primary prevention of SCD should only be implanted in patients with LVEF<30%, thus identifying a population of patients with 30%≤LVEF ≤35% that might not benefit from ICD implantation. *More recently Køber et al found that prophylactic ICD implantation was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care in patients with non-ischemic HF and LVEF ≤35% [Køber et al*. 2016]. *Furthermore, a pooled analysis of 1054 patients with class III HF included in SCD-HeFT, MADIT-II and DEFINITE trials, showed no significant survival benefit of ICD versus medical therapy [Barra et al*. 2016]*; while an ICD*

will prevent about 2 deaths per year for every 100 devices in patients with mild HF (NYHA class II) [Ponikowski et al. 2016]. *Thus*, it is expected that better risk stratification will lead to better patient selection improving the risk/benefit of ICD implantation.

The study will recruit patients with *stable HF who have been under guideline-directed medical therapy for at least 3 months and have 25%≤LVEF ≤35%.* Patients will be randomised to one of the 2 following groups. In one group, AdreView™ imaging will lead the decision of whether or not to implant an ICD and in the other it will not (the AdreView™ scan result will not be disclosed to the investigator). AdreView™ is a diagnostic radiopharmaceutical approved in the USA and several European countries for the identification of HF patients, NYHA class II and III with lower 1- and 2-year mortality risk. Patients randomised to the AdreView™ arm will have an ICD implanted within 45 days of randomisation if they are deemed to be at high risk according to the definition in Section 6.1 (AdreView™ H/M ratio [measured on an anterior planar image obtained at 3 hours and 50 minutes post-injection and calculated according to the instructions in the Imaging Manual] lower than 1.6). These patients should then face the same risks and benefits as those managed according to guidelines in the regular clinical setting.

Patients considered to be at low risk by AdreView™ imaging (i.e., those with a planar image H/M ratio≥1.6) will not receive an ICD, thus avoiding the exposure to complications; however they may face the risk that a potentially beneficial ICD implantation is withheld. GE Healthcare-sponsored study reports used for regulatory submissions (MBG311, MBG312 and MBG313; reports available upon request) have consistently showed a significant difference in all-cause and cardiac mortality between the high and the low risk groups in favour of the latter. These patients will also *continue to* receive the usual guideline-directed *optimal* medical therapy needed for their condition, including all the necessary follow-up visits and tests deemed necessary by the physician in charge. In addition, these patients will undergo a second AdreView™ H/M ratio determination 2 years after the first one in order to assess if their risk level has increased and ICD implantation is warranted. Moreover and as described in the protocol, the DSMB will regularly assess all safety aspects of the study.

Section 7.2, Inclusion Criteria, Inclusion Criteria (4) through (6)

Previously read:

(4) Heart failure NYHA classes II or III for symptoms, patients with ischemic or non-ischemic heart disease, eligible for ICD implantation as per each site's standard of practice.

(5) Non-ischemic dilated cardiomyopathy or ischemic heart disease of at least 3 months duration.

(6) 30%≤LVEF≤35%, performed within 3 months before or at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or

equivalent only, M-mode echocardiography is not accepted].
In case LVEF measurement is performed within 3 months before enrolment, measurement should be performed at least 40 days after a hospitalisation for HF or acute coronary syndrome (including myocardial infarction), and to be valid, method of measurement should be in accordance with the protocol and the imaging exam should be made available to the Sponsor in digital format.
In case several valid LVEF measurements are available, the closest to enrolment will be used for inclusion determination.

Now reads:

(4) Heart failure NYHA *class* II or III for symptoms, patients with ischemic or non-ischemic heart disease, eligible for ICD implantation as per each site's standard of practice.

(5) Non-ischemic dilated cardiomyopathy or ischemic heart disease of at least 3 months duration *receiving guideline-directed optimal medical therapy*.

(6) *25%*≤LVEF≤35%, performed within 3 months before or at time of enrolment, as measured by radionuclide ventriculography, or electrocardiogram [ECG]-gated SPECT myocardial perfusion imaging [MPI], or magnetic resonance imaging [MR], computed tomography [CT], or 3D or 2D echocardiography [Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted].
In case LVEF measurement is performed within 3 months before enrolment, measurement should be performed at least 40 days after a hospitalisation for HF or acute coronary syndrome (including myocardial infarction), and to be valid, method of measurement should be in accordance with the protocol and the imaging exam should be made available to the Sponsor in digital format.
In case several valid LVEF measurements are available, the closest to enrolment will be used for inclusion determination.

Section 7.3, Exclusion Criteria, Exclusion Criteria (7) and (16)

Previously read:

(7) Patient with chronic renal insufficiency defined as serum creatinine ≥3 mg/dl (or 265.2 µmol/L).

……..

(16) Patients previously enrolled in this study.

Now read:

(7) Patient with chronic renal insufficiency defined as serum creatinine ≥3 mg/dl (or ≥265.2 µmol/L).

……..

(16) Patients previously *randomized* in this study.

Section 8.1.1, AdreView™ (Iobenguane I^{123} Injection), First Paragraph

Previously read:

After randomisation to either the AdreView™ group or the SoC group, all patients will receive at least one intravenous injection of 10 mCi (370 MBq) of AdreView™. A ±10% tolerance of the nominal dose will be allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) in accordance with the Package Insert/Summary of Product Characteristics/Investigator's Brochure (IB). AdreView™ will be 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.

Now reads:

After randomisation to either the AdreView™ group or the SoC group, all patients will receive at least one intravenous injection of 10 mCi (370 MBq) of AdreView™. A ±10% tolerance of the nominal dose will be allowed, thus yielding an acceptable dose range of 9 to 11 mCi (333 to 407 MBq) in accordance with the Package Insert/Summary of Product Characteristics/Investigator's Brochure (IB). AdreView™ will be 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. *An administration volume of up to 15 mL may be used at sites where there are logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.*

Section 8.2, Method of Numbering Patients and Assigning Patients to Treatment Groups, First Paragraph

Previously read:

A unique allocation number will be assigned to each patient in successive order of entering the study after signing the informed consent document at each centre. No patient may be entered or screened (after failing to meet inclusion/exclusion criteria) into the study more than once. The allocation number will be unique for each patient in the study and will consist of 7 numbers in total: 3 numbers for the centre identification and 4 numbers for the patient identification at the centre (e.g., 0020001: first patient in centre No. 2). Please see the section on randomisation, Section 9.2.

Now reads:

A unique allocation number will be assigned to each patient in successive order of entering the study after signing the informed consent document at each centre. *Patients who fail one or more inclusion/exclusion criteria may be re-screened at a later date and, if subsequently found to be eligible, randomized into the study.* No patient may be *randomized* into the study more than once *(i.e., patients withdrawn after randomization may not be re-screened)*. The allocation number will be unique for each patient in the study and will consist of 7 numbers in total: 3 numbers for the centre identification and 4 numbers for the patient identification at the centre (e.g., 0020001: first patient in centre No. 2). Please see the section on randomisation, Section 9.2.

Section 8.3, Selection of Doses and Timing, Second Paragraph

Previously read:

AdreView™ will be 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.

Now reads:

AdreView™ will be 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. *An administration volume of up to 15 mL may be used at sites where there are logistical limitations to achieving delivery of IMP within the timelines required to meet the 370±10% MBq dose in a volume of 5 mL.*

Section 8.5, Prior and Concurrent Therapy, First Paragraph

Previously read:

Any medications taken by the patient within 30 days before and up to the end of study visit will be recorded in the eCRF along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognised dictionary of medical codes.

Now reads:

Any medications taken by the patient within 30 days before and up to the end of study visit will be recorded in the eCRF along with the indication and dosage*, including but not restricted to guideline-directed optimal medical therapy*. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication according to a current well-recognised dictionary of medical codes.

Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.

Section 9, Study Procedures, Table 1, Study Schedule of Events

Previously read:

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographic Information	X						
Medical/Surgical History	X			X	X		X
Concomitant Medications [b]	X			X	X		X
Pregnancy Test [c]	X					X	
Pre-Inclusion Events	X						
Physical examination (complete)	X						
Brief Physical examination				X	X		X
Blood samples for clinical laboratory evaluation	X						
Vital signs [d]	X			X	X		X
ECG	X						
Check LVEF values within the previous 3 months or perform LVEF assessment. [e]	X						
Assignment to study group		X					
AdreView™ Administration [f]			X			X	
Injection site monitoring			X			X	
Image Acquisition (Planar and SPECT) [e, g]			X			X	
ICD Implantation (if applicable) [h]			X				
ICD interrogation (if applicable)				X	X		X
AEs, SAEs and AdreView™-emergent AEs[i]	X	X	X	X	X	X	X
Data collection pertaining to primary and secondary endpoints			X	X	X	X	X

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [j]

*All procedures listed do not necessarily need to be performed during a single day

a Signed and dated informed consent must be obtained before eligibility assessments, including pregnancy test, are commenced.

b Recorded up to 30 days before screening.

c A serum or urine pregnancy test will be performed for all women of childbearing potential.

d Before vital signs are measured, the patient should be resting for at least 5 minutes. The same arm and position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contra-lateral to the site of AdreView™ administration whenever possible.

e Acceptable methods of LVEF assessment are radionuclide or contrast ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D 2D echocardiography (Simpson's or multidisc method or equivalent only). Image files will be sent to the Sponsor.

f AdreView™ will be administered to all patients. First AdreView™ administration should be performed in the 15 (+7) days post-randomisation. For the low-risk cohort only, a second AdreView™ administration should be administered at 2 years (±30 days) post-randomisation, unless patient withdraws prior to study termination or has already received an ICD. In this case the second AdreView™ scan will be offered before withdrawal becomes effective. Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

g At 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of planar images, and whenever possible followed by SPECT acquisition, according to the imaging manual. Patients with LVEF 30% to 35% with an H/M ratio ≥1.6 will have a second AdreView™ scan at 2 years (±30 days) post-randomisation.

h Patients in the randomised AdreView™ group who are assessed as high risk, and patients in the SoC group according to the standard of care in each investigational site derived from the local implementation of internationally accepted HF guidelines. ICD implantation should be performed according to clinical practice and should be performed within 45 days after randomisation.

i AdreView™-emergent AEs are defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

j Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

Now reads:

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [k]
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographic Information	X						
Medical/Surgical History	X			X	X		X
Concomitant Medications [b]	X			X	X		X
Pregnancy Test [c]	X		*X*			X	
Pre-Inclusion Events	X						
Physical examination (complete)	X						
Brief Physical examination				X	X		X
Blood samples for clinical laboratory evaluation	X						
Vital signs [d]	X			X	X		X
ECG	X						
Check LVEF values within the previous 3 months or perform LVEF assessment. [e]	X						
Assignment to study group		X					
AdreView™ Administration [f]			X			X	
Injection site monitoring			X			X	
Image Acquisition (Planar and SPECT) [e, g]			X			X	
ICD Implantation (if applicable) [h]			X				
ICD interrogation (if applicable) [i]				X	X		X
AEs, SAEs and AdreView™-emergent AEs[j]	X	X	X	X	X	X	X
Data collection pertaining to primary and secondary endpoints			X	X	X	X	X

Table 1 Study Schedule of Events

Variable	Screening / Enrolment Visit *	Randomisation	Post-Randomisation Procedures	Follow-Up Visit at 3 months post-ICD implantation (for patients with ICD implanted) (±15 days)	Follow-Up Visit at 6 months post-randomisation and then at least every 6 months (±15 days)	Second AdreView™ Administration at 2 years (±30 days) post-randomisation (low-risk cohort only)	End-of-Study Visit [k]

*All procedures listed do not necessarily need to be performed during a single day

a Signed and dated informed consent must be obtained before eligibility assessments, including pregnancy test, are commenced.

b Recorded up to 30 days before screening. *Investigators should record all guideline-directed optimal medical therapy. Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.*

c A serum or urine pregnancy test will be performed for all women of childbearing potential.

d Before vital signs are measured, the patient should be resting for at least 5 minutes. The same arm and position will be used each time vital signs are measured for a given patient and blood pressure will be measured from the arm contra-lateral to the site of AdreView™ administration whenever possible.

e Acceptable methods of LVEF assessment are radionuclide or contrast ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D 2D echocardiography (Simpson's or multidisc method or equivalent only). Image files will be sent to the Sponsor.

f AdreView™ will be administered to all patients. First AdreView™ administration should be performed in the 15 (+7) days post-randomisation. For the low-risk cohort only, a second AdreView™ administration should be administered at 2 years (±30 days) post-randomisation, unless patient withdraws prior to study termination or has already received an ICD. In this case the second AdreView™ scan will be offered before withdrawal becomes effective. Thyroid blocking should be performed before administration of AdreView™ in accordance with the Package Insert/Summary of Product Characteristics/IB and local regulations unless the patient has had a complete thyroidectomy.

g At 3 hours 50 minutes after administration of AdreView™, patients will undergo a 10-minute acquisition of planar images, and whenever possible followed by SPECT acquisition, according to the imaging manual. Patients with LVEF *25%* to 35% with an H/M ratio ≥1.6 will have a second AdreView™ scan at 2 years (±30 days) post-randomisation.

h Patients in the randomised AdreView™ group who are assessed as high risk, and patients in the SoC group according to the standard of care in each investigational site derived from the local implementation of internationally accepted HF guidelines. ICD implantation should be performed according to clinical practice and should be performed within 45 days after randomisation.

i *ICD interrogation does not need to be performed on the same day as the corresponding follow-up visit. ICD interrogation may be done remotely within ±5 days of the corresponding follow-up visit.*

j AdreView™-emergent AEs are defined as any AE which occurs within 24 hours after administration of AdreView™, and in addition any AE which occurs more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator.

k Patients will be enrolled and followed up until sufficient endpoints have accrued (247 primary endpoint events). All patients will then attend an end-of-study visit within 1 month.

Section 9.1, Screening / Enrolment Visit, Third Paragraph

Previously read:

At the screening visit, LVEF function determination will be performed in cases where a previous LVEF measurement is not available. If there is a previous LVEF measurement performed within 3 months of enrolment, the investigator will check that this measurement was performed when the patient had no hospitalisations for HF or acute coronary syndrome, or if such hospitalisation happened then the LVEF measurement was performed 40 days after the event. Acceptable methods for LVEF determination are as follows: radionuclide ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D or 2D echocardiography (Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted). LVEF images will be sent to the sponsor in electronic format.

Now reads:

At the screening*/enrolment* visit, LVEF function determination will be performed in cases where a previous LVEF measurement is not available. If there is a previous LVEF measurement performed within 3 months of enrolment, the investigator will check that this measurement was performed when the patient had no hospitalisations for HF or acute coronary syndrome, or if such hospitalisation happened then the LVEF measurement was performed 40 days after the event. Acceptable methods for LVEF determination are as follows: radionuclide ventriculography, ECG-gated SPECT MPI, MR, CT, or 3D or 2D echocardiography (Simpson's or multidisc method or equivalent only, M-mode echocardiography is not accepted). LVEF images will be sent to the sponsor in electronic format.

Section 9.1, Screening / Enrolment Visit, Bulleted List, Third Bullet

Previously read:

- Concomitant medications

Now reads:

- Concomitant medications*, including guideline-directed optimal medical therapy. Should any patients not be receiving guideline-directed optimal medical therapy at target dose per local guidelines, the investigator must document the reason(s) why in the source documents.*

Section 9.2, Randomisation, First and Second Paragraphs

Previously read:

Randomisation to the AdreView™ or SoC groups will be done remotely through an electronic data capture system (IWRS). Once the investigator has reviewed and properly entered the requested data, the electronic system will allocate the patient to the appropriate cohort should the patient be allowed to pursue the study. The primary randomisation is to one of 2 treatment methods in a 1:1 ratio stratified by enrolling centre.

Patients with 30%≤LVEF≤35% will be randomly assigned to the AdreView™ group or the SoC group via an IWRS. They will be scheduled for an AdreView™ scan to be performed within 15 (+7) days post-randomisation.

Now reads:

Randomisation to the AdreView™ or SoC groups will be done remotely through an electronic data capture system. Once the investigator has reviewed and properly entered the requested data, the electronic system will allocate the patient to the appropriate cohort should the patient be allowed to pursue the study. The primary randomisation is to one of 2 treatment methods in a 1:1 ratio stratified by enrolling centre.

Patients with *25*%≤LVEF≤35% will be randomly assigned to the AdreView™ group or the SoC group via an IWRS. They will be scheduled for an AdreView™ scan to be performed within 15 (+7) days post-randomisation.

Section 9.3, Post-Randomisation Procedures, New First Paragraph Added

Now reads:

All female patients (unless pre-menarchal, surgically sterile or post-menopausal) will undergo a serum or urine pregnancy test on the day of and prior to AdreView™ administration. AdreView™ dosing will only commence if the result is negative.

Section 9.3, Post-Randomisation Procedures, Fifth Paragraph (previously Fourth Paragraph)

Previously read:

Patients in the AdreView™ arm who are deemed at high-risk for all-cause and cardiovascular mortality (H/M ratio <1.6 as defined in Section 6.1) will undergo ICD device implantation. ICD implantation should be performed within 45 days of randomisation. Patients deemed to be at low risk (H/M ratio ≥1.6 as per Section 6.1) will receive guideline-directed medical therapy but will not undergo ICD implantation. In the low risk group, a second AdreView™ scan will

be performed at 2 years following the first scan, or in case of early withdrawal, prior to this withdrawal being effective.

Now reads:

Patients in the AdreView™ arm who are deemed at high-risk for all-cause and cardiovascular mortality (H/M ratio <1.6 as defined in Section 6.1) will undergo ICD device implantation. ICD implantation should be performed within 45 days of randomisation. Patients deemed to be at low risk (H/M ratio ≥1.6 as per Section 6.1) will *continue to* receive guideline-directed *optimal* medical therapy but will not undergo ICD implantation. In the low risk group, a second AdreView™ scan will be performed at 2 years following the first scan, or in case of early withdrawal, prior to this withdrawal being effective.

Section 9.4.1, Follow-Up Visit at 3 months (Only Patients Having Received ICD), Final Bullet Point

Previously read:

- ICD interrogation

Now reads:

- ICD interrogation*; may be performed remotely within ±5 days of follow-up visit.*

Section 9.4.2, Follow-Up Visits (All Patients), Final Bullet Point

Previously read:

- ICD interrogation (for those patients with an ICD)

Now reads:

- ICD interrogation (for those patients with an ICD)*; may be performed remotely within ±5 days of follow-up visit.*

Section 9.5, Second AdreView™ Administration

Previously read:

Patients in the low-risk AdreView™ group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. All female patients will undergo a serum or urine pregnancy test unless surgically sterile or post-menopausal prior to this scan. Should the H/M ratio fall under 1.6 and the patient is willing

and eligible for ICD implantation, he/she should receive an ICD. Should the patient withdraw prior to study termination the second AdreView™ scan will be offered prior to said withdrawal being effective.

Now reads:

Patients in the low-risk AdreView™ group will undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. All female patients will undergo a serum or urine pregnancy test unless *pre-menarchal*, surgically sterile or post-menopausal prior to this scan. Should the H/M ratio fall under 1.6 and the patient is willing and eligible for ICD implantation, he/she should receive an ICD. Should the patient withdraw prior to study termination the second AdreView™ scan will be offered prior to said withdrawal being effective.

Section 9.6, End of Study Visit, Final Bullet Point

Previously read:

- ICD interrogation (for those patients with an ICD)

Now reads:

- ICD interrogation (for those patients with an ICD)*; may be performed remotely within ±5 days of follow-up visit.*

Section 10.2.12, AdreView™-emergent Serious Adverse Event Reporting

Previously read:

Any AdreView™-emergent SAE must be forwarded immediately by the initial recipient at the Sponsor/CRO to one of the Global Pharmacovigilance mailboxes:

[redacted]

Now reads:

Any AdreView™-emergent SAE must be forwarded immediately by the initial recipient at the Sponsor/CRO *to the* Global Pharmacovigilance *mailbox*:

[redacted]

Section 11.3, Archiving, New final sentence added

Now reads:

National guidelines and regulations in individual countries should be followed as appropriate.

Section 12.3, Patient Demographics/Other Baseline Characteristics, First Bullet Point

Previously read:

- Number of patients enrolled.

Now reads:

- Number of patients *screened/*enrolled.

Section 12.5.2, Statistical Hypothesis, Model, and Method of Analysis, First Paragraph

Previously read:

This is an event-driven study. The primary efficacy analysis will take place after 247 instances of the primary efficacy endpoint have accrued. The primary efficacy endpoint will be analysed for non-inferiority. If the lower bound of the confidence interval exceeds 1, superiority will be claimed/ established.

Now reads:

This is an event-driven study. The primary efficacy analysis will take place after 247 instances of the primary efficacy endpoint have accrued. The primary efficacy endpoint will be analysed for non-inferiority. If the *upper* bound of the confidence interval *is less than* 1, superiority will be claimed/ established.

Section 12.5.4, Supportive Analyses

Previously read:

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (SoC vs AdreView™ group), LVEF, NYHA Classification, and BNP or NT proBNP as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

Now reads:

A sensitivity analysis on the primary efficacy analysis will be performed using the Cox proportional hazards model stratified by enrolling centre, with method of treatment guidance (*AdreView™ group vs. SOC*), LVEF, NYHA Classification, and BNP or NT proBNP as initial covariates. A stepwise regression with forward selection will be used to choose the final statistical model.

Section 12.8, Sample Size Calculation

Previously read:

Assumptions:

The all-cause mortality rate that is expected in the study has been estimated using the all-cause mortality rate observed in Study GE-122-016 at 36 months (internal report): 15.14 % for patients with 30%≤LVEF≤35% and having a H/M ratio<1.6, and 4.68% for patients with 30%≤LVEF≤35% and having a H/M ratio≥1.6. In addition, the following observations or assumptions were taken: in Study GE-122-016, 75 % of patients with 30%≤LVEF≤35% had a H/M ratio <1.6 and 25% had a H/M ratio ≥1.6. Referring to existing practice, only 15% of patients with 30%≤LVEF≤35% currently receive ICD. Accordingly, the number of patients who currently do not receive ICD but who will receive it according to protocol and the number of patients who currently receive ICD and who will not receive it according to protocol have been calculated. In addition, the all-cause mortality rate of patients currently not receiving ICD but who will receive according to protocol (85% of patients with H/M ratio<1.6 in the AdreView™ group) has been corrected to take into account the 31% reduction in all-cause mortality observed at 20 months in the MADIT II trial [Moss et al. 2012]. These assumptions led to a composite mortality rate of 9.5% in the AdreView™ group. The sample size is estimated with the hypothesis of not having a relative increase of mortality rate in excess of 20% and with the following assumptions:

- Alpha = 0.025, 1-sided.
- Statistical power = 80%.
- 1:1 randomisation to AdreView™ and SoC groups.
- H_0: $HR \geq HR_0$ vs H_1: $HR < HR_0$. $HR_0 = 1.20$.
- Assumed HR: 0.84.
- Accrual time: 18 months.
- The total study duration: 48 months.
- AdreView™ group survival rate at 36 months: 0.905.

Based on the above assumptions, the required total number of events will be 247, and the required total number of randomized patients will be 2,216.

The planned study accrual will be at least 2607 patients screened in order to randomize at least 2,216 patients in the study.

Now reads:

Assumptions:

The all-cause mortality rate that is expected in the study has been estimated using the all-cause mortality rate observed in Study GE-122-016 at 36 months (internal report). *It is assumed:*

	Patients with 25%≤LVEF≤30%		***Patients with 30%≤LVEF≤35%***	
	%	***Mortality Rate***	***%***	***Mortality Rate***
H/M ratio <1.6	*79%*	*20.25%*	*75%*	*15.14%*
H/M ratio ≥1.6	*21%*	*9.72%*	*25%*	*4.68%*

In addition, the following observations or assumptions were taken: *the ratio of patients with 25%≤LVEF≤30% vs 30%≤LVEF≤35% is expected to be 1:4 to account for the prior enrollment of only patients with 30%≤LVEF≤35%; the hazard ratio of patients with ICD implantation vs with usual care in the existing practice is 0.9 [Køber et al. 2016]*. Referring to existing practice, only 15% of patients with *25%*≤LVEF≤35% currently receive ICD. Accordingly, the number of patients who currently do not receive ICD but who will receive it according to protocol and the number of patients who currently receive ICD and who will not receive it according to protocol have been calculated. In addition, the all-cause mortality rate of patients currently not receiving ICD but who will receive according to protocol (85% of patients with H/M ratio <1.6 in the AdreView™ group) has been corrected to take into account the 31% reduction in all-cause mortality observed at 20 months in the MADIT II trial [Moss et al. 2012]. These assumptions led to a composite mortality rate of *11.34*% in the AdreView™ group *and 13.33% in the SoC group*. The sample size is estimated with the hypothesis of not having a relative increase of mortality rate in excess of 20% and with the following assumptions:

- Alpha = 0.025, 1-sided.
- Statistical power = 80%.
- 1:1 randomisation to AdreView™ and SoC groups.
- H_0: HR≥HR_0 vs H_1: HR<HR_0. HR_0 = 1.20.
- Assumed HR: 0.84.
- Accrual time: 18 months.
- The total study duration: 48 months.
- AdreView™ group survival rate at 36 months: *0.887*.

Based on the above assumptions, the required total number of events will be 247, and the required total number of randomized patients will be *2001*.

The planned study accrual will be at least *2354* patients screened in order to randomize at least *2001* patients in the study.

Section 12.10, Power for Analysis of Critical Secondary Variables, Final Paragraph

Previously read:

Thus, the sample size estimated for the primary efficacy endpoint is also adequate for the first key secondary endpoint (assuming 25% of patients in both the AdreView™ and SoC groups will have a H/M ratio ≥1.6 and therefore will not receive an ICD, an excess of 550 patients overall with a H/M ratio ≥1.6 is expected).

Now reads:

Thus, the sample size estimated for the primary efficacy endpoint is also adequate for the first key secondary endpoint (assuming *24*% of patients in both the AdreView™ and SoC groups will have a H/M ratio ≥1.6, *approximately 500* patients overall with a H/M ratio ≥1.6 is expected).

Section 14, References

Additional References Added:

Barra S, Providencia R, Agarwal S. Do we need further clinical-effectiveness estimates to support the use of primary prevention implantable cardioverter-defibrillators in New York Heart Association class III patients? Int J Cardiol. 2016;203:184-6

Bennett M, Parkash R, Nery P et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society 2016 Implantable Cardioverter-Defibrillator Guidelines. Canadian Journal of Cardiology 33 (2017) 174e188.

Golwala H et al. Implantable Cardioverter-Defibrillator for Nonischemic Cardiomyopathy: An Updated Meta-Analysis. Circulation. 2017;135(2):201-203

Køber L et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016;375(13):1221-30

McMurray JJ. The ICD in Heart Failure - Time for a Rethink? N Engl J Med. 2016;375(13):1283-4.

O'Day K et al. Cost-Effectiveness Analysis of Iodine-123 Meta-Iodobenzylguanidine Imaging for Screening Heart Failure Patients Eligible for an Implantable Cardioverter Defibrillator in the USA. Appl Health Econ Health Policy. 2016;14(3):361-73

Ponikowski P et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200

SIGNATURE PAGE

GE-122-020 CPR REV A02

Responsible Author:

Date (UTC):	Signed by:	Justification:
11-May-2017 12:19:29	[redacted]	Approved
11-May-2017 14:16:42	[redacted]	Approved

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