STATISTICAL ANALYSIS PLAN   **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**

Version: **1.0**

This Statistical Analysis Plan was prepared by the following personnel:

Name: ████████████

Title: Director, Biostatistics

Company: H2O Clinical, LLC

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Abbreviations

Abbreviation	Term
AE	Adverse Event
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CEAC	Critical Events Adjudication Committee
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organisation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESC	Executive Steering Committee
HF	Heart failure
H/M	Heart-to-Mediastinal ratio
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
LVEF	Left Ventricular Ejection Fraction
MADIT	Multicentre Automatic Defibrillator Implant Trial
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-inferiority
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCD	Sudden Cardiac Death
SD	Standard Deviation
SoC	Standard of Care
SPECT	Single Photon Emission Computed Tomography
WHO-DD	World Health Organization Drug Dictionary

1   INTRODUCTION

This document presents the statistical analysis plan (SAP) for GE Healthcare Protocol GE-122-020, an event-driven Phase IIIb, multicentre, randomised, clinical study to demonstrate the efficacy of AdreView™ imaging for appropriately guiding the decision of implantable cardioverter defibrillator (ICD) implantation, in New York Heart Association (NYHA) class II and III Heart Failure (HF) patients with 25%≤ left ventricular ejection fraction (LVEF) ≤35%, and in particular, for identifying patients who are at low risk for sudden cardiac death (SCD) and who would not benefit, or may suffer harm, from implantation of an ICD device (ADMIRE-ICD).

This SAP will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

The analyses described are based on the study protocol amendment 2 (GE-122-020 CPR REV A02).

2   STUDY OBJECTIVES, DESIGN AND PROCEDURES

2.1   Objectives

The objectives of the study are as follows:

Primary Objective:

- 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 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 hospitalization 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 hospitalization, 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 hospitalization for cardiovascular cause;

  - The rate of all-cause hospitalization;

  - 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 hospitalizations, treatment of adverse events (AEs), and AdreView™ administration.

- A composite of the rate of hospitalization 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 hospitalization, lead and/or generator removal/replacement, inappropriate shocks, explantation). (AdreView™ group vs. SoC).

Exploratory Objectives:

- ███
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  ████████████████████████████████████

2.2   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 patients with $25\% \leq LVEF \leq 35\%$, 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 patient group assignment is presented in Figure 1. A schedule of study procedures is provided in Table 1.

Figure 1   Study Diagram
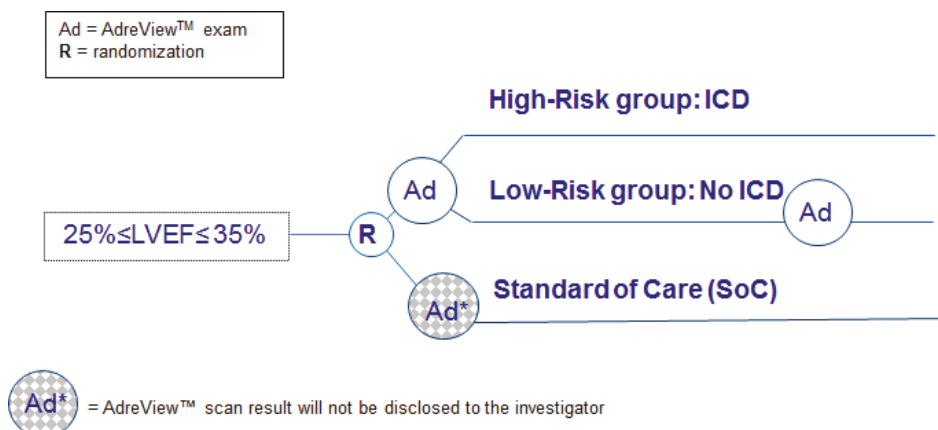
The study has been designed and endorsed by a Steering/Scientific Committee composed of world leaders in HF and arrhythmia management. Three committees have been formed in order to ensure proper scientific and ethical conduct of the study:

- An Executive Steering Committee (ESC) oversees the conduct of the study and makes recommendations to the Sponsor based on the outputs of the other 2 committees;

- A Critical Events Adjudication Committee (CEAC) adjudicates the study endpoints;

- A Data Safety Monitoring Board (DSMB) oversees the overall study safety.

The endpoints in this study are directly related to the health outcomes in both randomised groups. They are standardized 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 sets 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 are allowed to participate as site investigators, recruiting physicians or be directly involved in the care of study patients.

The DSMB acts 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 was to be conducted at approximately 130 centres in the USA, Canada and Europe. It was projected that at least 2354 patients should be screened (taking into account approximately 15% screen failure rate) in order to include at least 2001 patients in the study.

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

Patients with 25%≤LVEF≤35%, and meeting all other inclusion criteria and not meeting any of the exclusion criteria, were enrolled and randomly assigned to the AdreView™ group or the SoC group in a ratio of 1:1. All patients were to be scheduled for an AdreView™ scan. The results of the AdreView™ scan in the SoC group were to remain blinded to the investigator to avoid any influence in the decision of implanting an ICD. The binary assessment of risk (i.e., either high or low) was made for the AdreView™ patient group based on the H/M measurement made by the site personnel on the AdreView™ planar image (i.e. H/M <1.6 was high risk vs H/M ≥ 1.6 was low risk). Only the high/low risk classification was made known to the investigator and as such was used to determine ICD implantation in the AdreView group per protocol. Patients with AdreView™ H/M ratio <1.6 (high 1- and 2-year mortality risk) were to undergo ICD device implantation. Patients with AdreView™ H/M ratio ≥1.6 (low 1- and 2-year mortality risk) continued to receive guideline-directed optimal medical therapy according to clinical standard practice and did not undergo ICD implantation initially, but could receive an ICD at a later stage should they develop further symptoms and after assessment by the investigator. Patients in this latter group were to undergo a second AdreView™ scan (planar and possibly SPECT) 2 years post-randomisation for purposes of re-stratification. Patients allocated to the SoC group were to undergo ICD implantation and to be managed and followed up in accordance with internationally accepted HF guidelines.

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

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

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]
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

*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.

2.3 Sample Size

The all-cause mortality rate that is expected in the study was 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 Multicentre Automatic Defibrillator Implant Trial (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 was estimated with the hypothesis of not having a relative increase of mortality rate in excess of 20% in the AdreView™ group compared with the SoC group 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 was 247, and the required total number of randomised patients was 2001. The planned study accrual was at least 2354 patients screened in order to randomise at least 2001 patients in the study.

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 hospitalization 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 hospitalization, 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 would range from 156 to 486 patients overall with a H/M ratio ≥1.6. Thus, the sample size estimated for the primary efficacy endpoint was 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 was expected).

2.4   Interim Analysis

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

Additionally, during the course of the trial the DSMB could 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, the 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 Contract Research Organisation (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.

However, no interim analyses for futility or efficacy will be performed, because the sponsor decided to terminate the study early. At the time that the sponsor decided to terminate the study, the DSMB had not made any recommendation to terminate the study due to safety issues

2.5   Randomisation and Blinding

To ensure appropriate distribution of variables that may affect the primary endpoint, the primary randomisation was stratified by enrolling centre.

Neither patients nor site personnel (including the on-site AdreView™ scan reviewer) could be blinded to group assignment. Sites had to know whether patients were randomised to the AdreView™ or SoC groups in order to use the results of the scans in the AdreView™ group. However, the clinical investigator remained blinded to the values of H/M ratio obtained from the AdreView™ planar scan.

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

3   STUDY ENDPOINTS

3.1   Efficacy Endpoints

3.1.1   Primary Endpoint

The primary endpoint is all-cause mortality.

3.1.2   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.

3.1.3 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 all-cause hospitalization and the clinical and healthcare resource utilization data) will be reviewed and validated by the CEAC for all patients.

3.2 Safety Endpoints

- Clinical laboratory parameters: serum biochemistry and haematology

- 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, serious AEs [SAEs], and AdreView™-emergent AEs)

4 ANALYSIS POPULATIONS

4.1 Definition for Analysis Populations

Unless otherwise specified, all the endpoints will be analysed by study arm (the AdreView™ group or the SoC group) which is the group at the time that patient was randomised.

4.1.1 Safety Analysis Set (Safety Population)

The safety analysis set comprises all patients who signed the inform consent form and met all of the inclusion criteria and none of the exclusion criteria.

4.1.2 Full Analysis Set (Efficacy Population)

The full analysis set is defined as patients in the safety analysis set who were randomised to the AdreView™ group or the SoC group.

5 ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the ICH M2 Guidelines [ICH 2008]. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;

2. SAS® program name, including the path that generates the output;

3. Any other output-specific details that require further elaboration.

In general, tables will be formatted with columns displaying findings based on the study arm for all patients. The summary tables will clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

Supportive individual Patient Data Listings, as a minimum, will be sorted and presented by the study arm, patient number, and visit date, if applicable.

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics for categorical variables will consist of the number and percentage of responses in each level. The number and percentage of responses will be presented in the form XX (XX.X%).

- Summary statistics for continuous variables will consist of the sample size (n), mean, median, standard deviation (SD), first quartile, third quartile, minimum, and maximum values.

- All mean, median and quartile values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- All p-values, if applicable, will be rounded to 4 decimal places. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999'. Two-sided P-values < 0.05 will be considered to be statistically significant unless otherwise specified.

- All summary tables will include the analysis population sample size (i.e., number of patients).

- Study Day 1 is defined as the date at which the patient was randomised. All study days are determined relative to Day 1.

- Study days prior to Day 1 will be calculated as:

  o Study Day = Assessment Date – Randomisation Date

- Study days after Day 1 will be calculated as:

  o Study Day = Assessment Date – Randomisation Date + 1.

- Baseline values will be defined as the last non-missing value recorded prior to randomisation.

- Change from baseline will be calculated as follows:
  Change = Post-baseline value - baseline value.

- All pre- and post-enrolment assessments including unscheduled or repeat assessments will be included in the data listings.

- Date variables will be formatted as YYYY-MM-DD for presentation.

- Tables, figures, and listings will be presented in landscape orientation.

- SAS® Version 9.4 or higher will be the statistical software package used for all data analyses.

Definition of Analysis Windows

There are no visit windows for this study. For the statistical analyses, data will be analyzed by the nominal visit that was collected on the electronic case report form (eCRF).

Unscheduled visits will not be used in the by-visit analysis, but will be used for the following where appropriate: 1) derivations of baseline/last on-treatment measurements; 2) derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses; 3) data listings.

Definition of Missing Data Imputation

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation.

Pooling of Enrolment Site

Due to the small number of patients that may have been enrolled at each study site, country will be included in the model as the stratification factor instead of the enrolment site. If there are countries that enroll only a small number of patients, the sponsor will review and provide the appropriate pooling strategy.

5.1   Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

5.1.1   Demographic and Baseline Characteristics

Demographic information (age, height, weight, and body mass index [BMI]) will be summarized using descriptive statistics and p-values of the comparison between SoC and AdreView™ group will be presented by performing a two sample t-test. Gender and race will be summarized by counts and percentages and p-values of the comparison between the SoC and AdreView™ group will presented by using a Chi-square test.

5.1.2   Medical and Surgical History

Medical and surgical history data will be summarized and presented using category and conditions/procedures as captured on the eCRF. The number and percentage of patients with a

particular condition/procedure will be summarized for each study arm. Patients reporting more than one condition/procedure within a category will be counted only once for that category.

5.1.3 Prior and Concomitant Medications

Any medications taken by the patient within 30 days before screening and up to the end of study visit will be summarized by counts and percentages using the World Health Organization Drug Dictionary (WHO-DD) March 2016 version, and grouped by primary and secondary classes, if applicable.

A prior medication is defined as any medication taken prior to the first AdreView™ administration. A concomitant medication is defined as any medication continued or newly taken after the first AdreView™ administration. If a medication cannot be classified as "prior" or "concomitant" because of missing/incomplete start and/or end dates, it will be classified as both prior and concomitant.

In addition, number of medications related to Guideline-Directed Optimal Medical Therapy (GDMT) at screening will be summarized and p-values of the comparison between the SoC and AdreView™ group will presented by using a Chi-square test.

5.2 Patient Disposition

The number of patients for each of the following categories will be summarized.

- Patients screened/enrolled

- Patients included in the safety analysis set

- Patients included in the full analysis set

- Patients withdrawn from the study and the reason for withdrawal

5.3 Study Drug Exposure

For each AdreView™ administration, the dose (MBq) and volume (mL) will be summarized using descriptive statistics.

5.4 Efficacy Analysis

5.4.1 General Considerations

The analysis of the efficacy data will be based on the efficacy population.

5.4.2 Primary Efficacy Analysis

The primary endpoint is the hazard ratio of the all-cause mortality between the AdreView™ group and SoC. The primary efficacy endpoint will be analyzed for non-inferiority (NI) with the NI boundary equal to 1.2. If the upper bound of the confidence interval for the HR is less than 1, superiority will be claimed/ established.

The hypothesis testing for the primary objective is:

H_0: hazard ratio (HR) (AdreView™ group / SoC) $\geq$ 1.2

Ha: HR (AdreView™ group / SoC) < 1.2

Cox proportional hazards model stratified by country, with study arm (AdreView™ group vs SoC) as the only covariate will be performed at a 1-sided alpha value of 0.025 for the primary endpoint.

Kaplan-Meier plot will be presented by method of treatment guidance. Patients who are still alive at the time of data base lock will be censored at the last known-alive date.

5.4.3 Secondary Efficacy Analyses

5.4.3.1 Key Secondary Endpoints Analyses

- 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) and a composite rate of 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 (odds ratio of AdreView^{TM} vs SoC < 1.0). These proportions will be compared between the patients with H/M $\geq$1.60 in the AdreView™ group and the patients with H/M $\geq$1.60 in the SoC group, using the Cochran-Mantel-Haenszel (CMH) test stratified by country, using a 2-sided alpha value of 0.05.

- Cardiac death. The occurrence of this event will be analysed using a Cox proportional hazards model as described in the primary efficacy analysis (NI, using an NI margin of 1.20). Kaplan-Meier plot will be presented by method of treatment guidance. Patients who were alive or who had died from other than cardiovascular causes at the time of data base lock will be censored at the last known-alive date.

- Rate of hospitalisation for cardiovascular cause. The odds ratio of this rate will be compared between the AdreView™ and SoC groups using the CMH test stratified by country (NI, using an NI margin of 1.20).

- Rate of all-cause hospitalisation. The odds ratio of this rate will be compared between the AdreView™ and SoC groups using the CMH test stratified by country, (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 first occurrence of these events will be analysed using a Cox proportional hazards model as described in the primary efficacy analysis (NI, using an NI margin of 1.20). Kaplan-Meier plot will be presented by the study arm. Patients who had not experienced any of the events at the time of data base lock will be censored at the last known-alive date.

5.4.3.2 Additional Secondary Endpoints Analyses

- 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 (NI, using an NI margin of 1.20). Patients who had not experienced syncope at the time of data base lock will be censored at the last known-alive date.

- 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. The clinical data may be summarised and compared between the AdreView™ and SoC groups. The healthcare resource utilization data will not be analysed due to early termination.

- 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 using a Cox proportional hazards model as described in the primary efficacy analysis. These data will be analysed with a superiority analysis (HR of AdreView^{TM} vs SoC < 1.0), using a 2-sided alpha value of 0.05. Kaplan-Meier plot will be presented by method of treatment guidance. Patients who had not experienced any of the events at the time of data base lock will be censored at the last known-alive date.

- The rate of ICD implantation and ICD explanation will be summarized for each study arm. In addition, the reasons of ICD implantation and ICD explanation will also be summarized. The odds ratio of the rate of rate of ICD implantation and ICD explanation will be compared between the AdreView™ and SoC groups using the CMH test stratified by country.

5.4.4   Handling of Multiplicity

Due to early termination of the study by the sponsor, the sample size is not sufficient for the hierarchical hypothesis testing. All of the secondary endpoints will be analyzed inferentially as reference only.

5.5   Safety Analysis

5.5.1   General Considerations

The safety variables to be analyzed include all AEs occurring after informed consent, all study-emergent AEs, AdreView™-emergent AEs, SAEs, vital sign data, physical examination results, clinical laboratory test data, and electrocardiographic data. All safety analyses will be performed by study arm in the safety population. All safety data will be listed by study arm and patient number.

5.5.2   Analysis of Adverse Events

All AEs occurring after informed consent were recorded on the eCRF. A study-emergent AE is defined as an AE that occurred after randomisation. An AdreView™-emergent AE is defined as an AE that occurred or worsened within 24 hours after administration of AdreView™ and in addition any AE which occurred more than 24 hours after administration of AdreView™ for which a causal relationship is assumed by the investigator. If the date of occurrence of an AE cannot be determined relative to date of randomisation, it will be assumed to be both study-emergent and AdreView™-emergent. AEs will be mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 19.0.

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

5.5.2.1   Overall Summary of Adverse Events

The number and percentage of patients experiencing AEs will be summarized, and p-values comparing the two study arms will be provided for the following AE categories:

- Any study-emergent AEs;
- Any serious study-emergent AEs;
- Any AdreView™-emergent AEs;
- Any serious AdreView™-emergent AEs;
- Any study-emergent AEs related to AdreView™;

- Any AdreView™-emergent AEs related to AdreView™;
- Any study-emergent AEs related to ICD implantation;
- Study-emergent AEs by maximum intensity;
- AdreView™-emergent AEs by maximum intensity;
- Any study-emergent AEs leading to discontinuation from the study;
- Any AdreView™-emergent AEs leading to discontinuation from the study;
- Any AdreView™-emergent AEs leading to death;
- Any study-emergent AEs leading to death.

In addition, number of AEs, number of study-emergent AEs, and number of AdreView™-emergent AEs will be provided.

5.5.2.2 Summary of Adverse Events by System Organ Class and Preferred Term

Summaries of study-emergent AEs, AdreView™-emergent AEs, study-emergent SAEs, and AdreView™-emergent SAEs by system organ class and preferred term will be the primary presentations of the AE data. Patients will be counted only once at the system organ class level and will be counted once for each applicable preferred term; multiple occurrences of the same preferred term for a patient will be counted only once. System organ classes, and preferred terms within a system organ class, will be displayed alphabetically. In addition, summaries of common (>5% of patient in either AdreView™ or SoC group) study-emergent AEs, AdreView™-emergent AEs, study-emergent SAEs, and AdreView™-emergent SAEs by preferred term will be sorted in decreasing overall frequency.

5.5.2.3 Summary of Adverse Events by System Organ Class and Preferred Term with Respect to Event Intensity

All serious and non-serious AEs will be assessed for intensity. The intensity of all AEs will be graded as mild, moderate, or severe using the definitions:

Mild: Tolerable

Moderate: Interferes with normal activity

Severe: Incapacitating (causes inability to perform usual activity or work).

Summaries of study-emergent AEs, AdreView™-emergent AEs, study-emergent SAEs, and AdreView™-emergent SAEs by system organ class and preferred term with respect to event intensity will be provided. Patients with multiple AE/SAEs of the same system organ class or preferred term will be summarized at the maximum severity reported within that system organ class or preferred term. Patients having an AE/SAE with missing intensity will have the intensity imputed as severe. The number and percentage of patients experiencing study-

emergent AEs/SAEs or AdreView™-emergent AEs/SAEs for each system organ class and preferred term will be displayed.

5.5.2.4   Assessment of Relationship to AdreView™ or ICD Implantation

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

- Before AdreView™ Administration

- After AdreView™ Administration - Relationship to AdreView™ is not Suspected

- After AdreView™ Administration - Relationship to AdreView™ is Suspected

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

- Before ICD Implantation

- After ICD Implantation - Relationship to ICD Implantation is not Suspected

- After ICD Implantation - Relationship to ICD Implantation is Suspected

- Not Applicable

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

A summary of study-emergent AEs, AdreView™-emergent AEs, study-emergent SAEs, and AdreView™-emergent SAEs by system organ class, preferred term and relationship to AdreView™ or ICD Implantation will be provided. This table will display only those study-emergent or AdreView™-emergent AEs/SAEs that are determined to be related to AdreView™ or ICD Implantation. Patients with multiple occurrences of the same system organ class or preferred term will be summarized using the event with the strongest relationship to AdreView™ or ICD Implantation. Patients having an AE/SAE with missing relationship will have the relationship imputed as related. The number and percentage of patients experiencing study-emergent AEs/SAEs or AdreView™-emergent AEs/SAEs for each body system and preferred term will be displayed.

5.5.2.5   Summary of Adverse Events Leading to Discontinued from Study by System Organ Class and Preferred Term

Summaries of study-emergent AEs/SAEs and AdreView™-emergent AEs/SAEs leading to study discontinuation by system organ class and preferred term will be provided.

5.5.2.6 Summary of Adverse Events Leading to Death by System Organ Class and Preferred Term

Summaries of study-emergent AEs/SAEs and AdreView™-emergent AEs/SAEs leading to Death by system organ class and preferred term will be provided.

5.5.2.7 Summary of Adverse Events by System Organ Class and Preferred Term with Respect to the Treatment Given for the Event

Summaries of study-emergent AEs/SAEs and AdreView™-emergent AEs/SAEs by system organ class and preferred term with respect to the treatment given for the event will be provided.

5.5.3 Analysis of Laboratory Data

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

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)	

Clinical laboratory tests were performed at only the screening/enrolment visit. Descriptive statistics will be displayed for the observed values by each study arm.

5.5.4 Analysis of Vital Signs

Vital sign variables are weight, BMI, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and pulse oximetry. Table 3 presents the criteria for vital sign normal limits.

Table 3   Criteria for Normal Limits for Vital Signs

Vital Sign Parameter	Normal Limits	
	Low	High
Systolic BP (mmHg)	85	140
Diastolic BP (mmHg)	60	90
Heart Rate (bpm)	60	100
Respiration 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 analyzed retrospectively by the Sponsor, at which time height is taken into account.

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 summarized 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 (i.e. 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). Shift tables based on the normal range will be prepared.

5.5.5   Analysis of ECG Parameters

A standard 12-lead ECG was performed at only the Screening/Enrolment visit. Table 4 presents the criteria for ECG normal limits.

Table 4   Criteria for Normal Limits for ECGs

ECG Variable	Normal Limits (ms)	
	Low	High
PR interval	120	200
QRS interval	50	100
RR interval	600	1000
QT interval (gender not specified)	-	≤440
QTc interval[a] (gender not specified)	-	≤440

[a] No lower boundary set for QTc.

The QT interval will be corrected using Fridericia's formula and Bazett's formula as follows:

- Fredericia's formula: $QTcF = QT/RR^{1/3}$
- Bazett's formula: $QTcB = QT/RR^{1/2}$

Descriptive statistics will be displayed for the observed values by each enrolment group and p-values of the comparison between SoC and AdreView™ group will be presented by using two sample t-test. The occurrence of observed values outside the normal limits will be summarized by counts and percentages.

Overall investigator interpretation of ECG will be categorized as normal, abnormal (Not Clinically Significant) and abnormal (Clinically Significant) and will be summarized by counts and percentages.

5.5.6 Analysis of Physical Examinations

The results of the physical examinations at baseline (complete physical examinations) and at each post-randomisation time point (brief physical examinations) will be summarized.

6 SPECIAL STATISTICAL TOPICS

This study was discontinued prematurely by the sponsor. Due to the early termination of the study, the following objectives for the study will not be performed and will be evaluated in the future if needed.

- The healthcare resource utilization data including ICD implantation, all hospitalizations, treatment of AEs, and AdreView™ administration

- Statistical relationship between AdreView™ global and/or regional distribution quantified on Single Photon Emission Computed Tomography (SPECT) images with the same clinical outcomes as with planar H/M ratio

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SIGNATURE PAGE

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Signed By: ████████████████ Date of signature: 20-Jun-2018 11:56:57 GMT+0000	Justification: Approved Role: Head of Biometrics