STUDY CODE: IPTL01 **STUDY NAME: LEVEA**

STUDY TITLE:

clinical evaluation of LEft VEntricular Auto threshold algorithm

CLINICAL INVESTIGATION PLAN

Version N° 1.0 **Date: 29 September 2016**

Investigational Feature: "In-Clinic LVAT" Algorithm

	Name	Function	Signature	Date
Prepared by	Hanan FAWAZ	Project Manager		Sept 30, 2016
Verified by	Tina LARRACAS	Safety Office Director		Oct 6 2016
Verified by	Debarshi DEY	Senior Biostatistician		Sep 30, 2016
Verified by	Aurelie WINGERT-FUCHS	Clinical QA Leader		Oct 3, 2016
Verified by	Amel AMBLARD	Clinical Research Director		Oct 3rd 2016
Approved by	Jude CADET	CRM Clinical Affairs Director		Oct 6, 2016
Approved by	Pr. Jacques MANSOURATI	Coordinating Investigator		oct 12, 2016

REVIEWED BY:

Luc Verhees – VP Global Clinical Affairs; Director; Giacomo Mordenti – Global Biometrics Director; Jason Peters – Head Global Data Management; Ella Guillaume – Senior Clinical Data Manager; Kristine Klinger – PMO and Clinical Services; Gerhard Askamp – Program Manager Anne Rousseauplasse – Scientific Communication Manager CRM; Antoine Vaugelade - Clinical Quality Assurance Associate; Nicolas Rosset – Clinical System Manager; Jennifer Oudry – Clinical Research Engineer; Marie-Anne Euzen - Clinical Research Engineer.

DOCUMENT HISTORY

Version	Date	Section(s)	Description of modifications
1			Initial Release

INVESTIGATOR SIGNATURE PAGE

The Sponsor is required by regulations to obtain a signed agreement from each participating Principal Investigator (PI) for any used version of the Clinical Investigation Plan (CIP).

By signing the CIP, the PI certifies he/she reviewed the document and agrees to its content.

Non-disclosure

During conduct of the study, you may acquire knowledge of the performance of the device in the study through your own investigation and through reports of other investigators. This information is valuable to the Sponsor and is considered confidential in nature. By signing this CIP, you agree not to disclose any confidential information to any person other than one involved in the study without prior written approval from the Sponsor. The Sponsor retains the right to publish the results of the study.

Last name:	
First name:	
Name of institution:	
Signature:	**Date:** D D M M M Y Y Y Y

One copy for the Principal Investigator, one copy for the Sponsor.

NAMES AND ADDRESSES

COORDINATING INVESTIGATOR	**Name :**	Jacques Mansourati, MD
	Address:	Centre Hospitalier Régional Universitaire 2 Avenue Maréchal Foch 29200 Brest, France
	E-mail:	jacques.mansourati@chu-brest.fr

SPONSOR	**Company name:**	SORIN CRM SAS
	Address:	Parc d'Affaires NOVEOS 4 avenue Réaumur 92143 Clamart Cedex, France
	Telephone:	+ 33 (0)1 46 01 33 33
	Fax:	+ 33 (0)1 46 01 34 65

STUDY MANAGER	**Name:**	Hanan Fawaz
	Address:	Parc d'Affaires NOVEOS 4 avenue Réaumur 92143 Clamart Cedex, France
	Telephone:	+ 33 (0)1 46 01 89 01
	E-mail:	hanan.fawaz@livanova.com

SAFETY OFFICER	**Name:**	Tina Larracas, MD
	Address:	Parc d'Affaires NOVEOS 4 avenue Réaumur 92143 Clamart Cedex, France
	Telephone:	+ 33 (0)1 46 01 34 06
	E-mail:	tina.larracas@livanova.com

TABLE OF CONTENTS

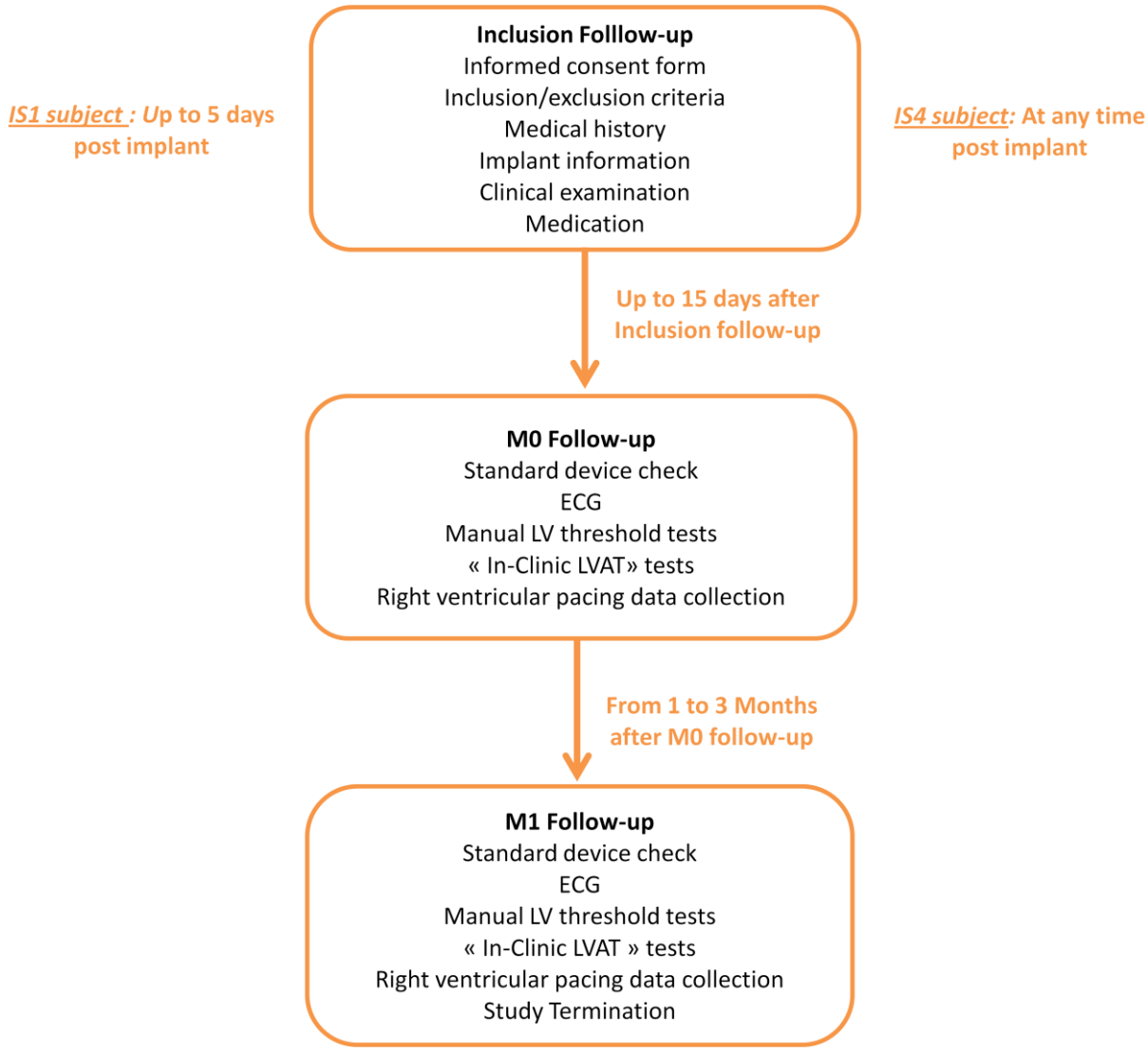
1. **SYNOPSIS**

Title:	Clinical evaluation of left ventricular auto threshold algorithm.
Primary objective:	The primary objective of the study is to assess the success rate of left ventricular threshold value identified automatically by "In-Clinic LVAT" feature compared to manual threshold test performed by physician.
Study design:	Multicenter, prospective, non randomized, confirmatory study.
Number of subjects and sites:	59 subjects will be enrolled in approximately 12 sites in Europe.
Study duration:	Approximately 6 months corresponding to 3 months of inclusion period and 3 months of follow-up.
Study population:	Heart failure subjects indicated for cardiac resynchronization therapy (CRT) device implantation according to the current guidelines of the European Society of Cardiology (ESC).

Inclusion criteria:	Subjects who meet all the following criteria at the time of enrollment may be included:
	• Subject already implanted (de-novo, upgrade or replacement) according to the relevant ESC Guidelines [1]:
	  ○ With IS1 Platinium SonR CRT-D (models 1811, 1841, CE marked) for maximum of 5 days, or
	  ○ With IS4 Platinium SonR CRT-D (model 1844, CE marked).
	• Right atrial, right and left ventricular leads must be implanted. Only bipolar or quadripolar for left ventricle lead.
	• Reviewed, signed and dated informed consent.

Exclusion criteria:	Subjects who meet any one of the following criteria at the time of enrollment cannot be included in the investigation: • Subject included in another clinical study that could confound the results of this study; • Malfunction or dislodgment of right atrial, right and left ventricular implanted leads; • Subject diagnosed with permanent atrial fibrillation; • Known pregnancy; • Minor age; • Under protection or guardianship; • Unavailability for scheduled follow-up or refusal to cooperate.

Device description:	Platinium SonR CRT-D CE marked: • DF1/IS1 model 1811 • DF4/IS1 model 1841 • DF4/IS4 model 1844 Orchestra Plus programming system with 2.54.C1 (or upgraded version) clinical SmartView version.
Primary endpoint:	The primary endpoint of the study is the success rate of "In-Clinic LVAT" function. The success is defined by a LV threshold value identified automatically by "In-Clinic LVAT" feature equivalent to the manual threshold test value performed by physician on at least 90% among complete tests (performance goal).
Statistical considerations:	The purpose of this study is to determine if the success rate of the "In-Clinic LVAT" feature is at least 90%. The statistical analysis of primary endpoint will be performed on all eligible subjects versus a performance goal. A sample size of at least 231 evaluable LV pacing vectors will provide 80% power to reject the trial null hypothesis by using a one-sided alpha 2.5% and assuming an expected success rate of 95%. As each subject can provide data on 5 different pacing vectors, 47 (~231/5) subjects are needed for the analysis. Accounting for a global attrition rate of 20%, 59 subjects shall be enrolled. A one-sided exact binomial test for proportion at 2.5% level of significance (alpha) will be performed to test the null hypothesis for the primary endpoint. The null hypothesis will be rejected if the p-value is less than 0.025. The estimate of the success rate will be presented along with exact 95% confidence interval (CI) (Clopper & Pearson, 1934). [2] The primary analysis is based on at least 231 complete LV Vector Tests provided by the algorithm and collected at M0. If data at M0 is unavailable, then corresponding data collected at M1 will be considered.



STUDY FOLLOW-UPS AND ASSESSMENTS

Follow-ups	Acceptable period follow-up	Assessments
Inclusion	**<u>IS1 subject</u>: Up to 5 days post-implant** **<u>IS4 subject</u>: at any time after implant**	○ Signed informed consent ○ Inclusion/exclusion criteria ○ Medical history ○ Implant information ○ Clinical examination including vital signs and NYHA classification ○ Concomitant Medication
M0	**Up to 15 days after inclusion follow-up**	○ Check device electrical performances ○ Manual LV pacing threshold tests on: ▪ 5 different LV vectors common to IS1 and IS4 for all subjects ▪ 4 dedicated IS4 LV pacing vectors for subject implanted with IS4 LV lead *Optional manual threshold tests on additional LV pacing vectors could be performed under physician discretion*. ○ ECG record: ▪ Spontaneous rhythm ▪ Paced rhythm during "In-Clinic LVAT" in DDD A-test: 30 seconds recording corresponding to 10 seconds before launching the test and 20 seconds during the test ○ "In-Clinic LVAT" tests for all eligible LV pacing vectors in different pacing configurations: - DDD A-test (atrium overdrive) - DDD P-test (no atrium overdrive) - VVI ○ Right ventricular pacing data collection: A-test and P-test ○ Retrieve technical analysis electronic files ○ Report Adverse Events and Serious Adverse Events occurred during the testing procedure if any ○ Report device deficiency if any

M1	**From 1 to 3 months after M0 follow-up**	○ Check device electrical performances ○ Manual LV pacing threshold tests on: ▪ 5 different LV vectors common to IS1 and IS4 for all subjects ▪ 4 dedicated IS4 LV pacing vectors for subject implanted with IS4 LV lead *Optional manual threshold tests on additional LV pacing vectors could be performed under physician discretion*. ○ ECG record: ▪ Spontaneous rhythm ▪ Paced rhythm during "In-Clinic LVAT" in DDD A-test: 30 seconds recording corresponding to 10 seconds before launching the test and 20 seconds during the test ○ "In-Clinic LVAT" tests for all eligible LV pacing vectors in different pacing configurations: - DDD A-test (atrium overdrive) - DDD P-test (no atrium overdrive) - VVI ○ Right ventricular pacing data collection: A-test and P-test ○ Retrieve technical analysis electronic files ○ Report Adverse Events and Serious Adverse Events occurred during the testing procedure if any ○ Report device deficiency if any ○ Report Serious Cardiovascular Adverse Events occurred since last follow-up if any
Unscheduled	**If relevant**	○ Check device electrical performances ○ Report Serious Cardiovascular Adverse Events if any ○ Report device deficiency if any

2. SCIENTIFIC JUSTIFICATION

2.1. BACKGROUND

Anti-bradycardia stimulation therapy involves the delivery of controlled stimulation pulses to an atrial and/or a ventricular cavity, through pacing leads connected to a single or dual chamber pacemaker device. In case of cardiac resynchronization therapy (CRT), an additional pacing lead is implanted in a coronary sinus tributary vein in order to pace both right and left ventricles.

The pacing threshold test is a standard of care measurement, performed during each subject follow-up, in order to determine the minimum pacing energy required to induce a depolarization wave in the cavity called "capture". During this test, the amplitude and/or the width of the stimulation pulses are adjusted to optimize the energy delivered by the device.

Since 2011, new quadripolar left ventricular leads have been introduced in the market [3-6] offering more Left Ventricular (LV) pacing vectors. It became necessary for the physician to test all LV pacing vectors in order to select the optimal one according to the pacing threshold and/or presence/absence of undesirable phrenic nerve stimulation (PNS). The use of a quadripolar lead may therefore substantially increase the time needed to perform all tests and consequently the follow-up duration.

In order to facilitate the determination of all LV pacing vector thresholds and help the physician to identify the optimal parameter in a timely manner, new features are offered to manage automatically the pacing threshold tests [7-9].

Medtronic developed the VectorExpress™ left ventricular automated test [7] that is able to test up to 16 LV pacing vectors. The physician can then choose the optimal LV pacing vector corresponding to an appropriate capture threshold and impedance. Meanwhile, St Jude Medical developed the VectSelect Quartet™ LV pulse configuration [6, 8]. The feature automatically identifies tissue sites with the latest activation by inter ventricular conduction delays measurements and performs threshold testing, and enables marking of PNS. Boston Scientific Cardiac Resynchronization Therapy Defibrillator (CRT-D) devices offer PaceSafe Left Ventricular Automatic Threshold. The feature is designed to dynamically adjust the left ventricular pacing amplitude to ensure capture of the LV using a programmable safety margin. PaceSafe LVAT is only available in bipolar and unipolar LV pacing configurations and not in devices with quadripolar lead.

2.2. AVAILABLE CLINICAL DATA

2.2.1. *Data from similar features*

a. Medtronic LVCM

Left Ventricular Capture Management® (LVCM) algorithm is an automatic feature that monitors the pacing amplitude threshold and adjusts LV outputs. This function helps to ensure delivery of CRT, potentially save time in testing and measuring LV pacing thresholds during subject follow-up.

Therefore, it will automatically balance subject safety and device longevity. LVCM customizes LV pacing outputs to match the needs of individual subjects and analyze LV thresholds over time with trends reports. [10-13]

In the study of Crossley et al. [10], 134 subjects (130 analyzed) from 18 centers, already implanted with a CRT-D system, were enrolled in a clinical trial to evaluate the performance of the LVCM algorithm.

At each follow-up, threshold values were measured manually and with LVCM algorithm. The results were then compared on 307 complete threshold measurement pairs (manual and LVCM in-office tests) collected from 107 subjects for the primary endpoint analysis:

- The difference between LVCM in-office tests and manual threshold tests was within one step in 99.7% (306/307) of the attempts with a two-sided 95% confidence interval of [98.2%, 100.0%].
- LVCM in-office test was identical to the manual LV threshold test in 247 out of 307 attempts (80.72%).

b. Medtronic VectorExpress

In the study of Johnson et al. [7], the accuracy of an automated pacing capture thresholds algorithm for quadripolar left ventricular leads called VectorExpress was determined. This algorithm provides automatically the pacing threshold value on all selected LV pacing vectors. Evaluation was performed comparing both threshold values provided by the algorithm and measured manually.

Thresholds were measured for 780 of 992 vectors and at least one vector was measured in 62 of 65 subjects. Results were considered as equivalent if the difference of threshold value provided by manual test and the algorithm was:

- Within ± 0.5V if manual threshold is strictly inferior to 2.5 V, or
- Within ± 1.0V if manual threshold is between 2.5 V and 6.0 V.

The accuracy of the automatic algorithm VectorExpress compared to the manual pacing test was 95.3%.

c. Boston Scientific LVAT (Left Ventricular Auto Threshold)

The ELEVATE (Evaluation of LEft Ventricular Auto ThrEshold) study is an acute, prospective, multicenter, pilot study designed to characterize the performance of Boston Scientific LVAT (Left Ventricular Auto Threshold) feature, specifically the commanded mode of LVAT. The study compared the threshold value measured

manually to the one provided by LVAT feature using a surface ECG [14]. The commanded mode of LVAT enables to determine automatically the pacing threshold value of a LV pacing vector.

The LVAT algorithm was able to determine a threshold value in at least one of four LV pacing vectors in 69 of 70 (98.57%) subjects.

The accuracy of the LVAT-determined threshold value was quantified using two different metrics. The threshold determined by the algorithm and by the Corelab matched in 233 of 234 tests (99.5%). In addition, the comparison to the manual threshold value was considered as successful (meaning within two voltage steps) in 96.14% of cases.

Another clinical study sponsored by Boston Scientific is ongoing but not recruiting participants. This clinical trial is called Evaluation of Automatic Threshold Algorithms (CAPTIVATE): see https://clinicaltrials.gov. The study aims to evaluate the PaceSafe Right Ventricular Autothreshold (RVAT) and Left Ventricular Autothreshold (LVAT) features for AUTOGEN CRT-D devices. The accuracy of the algorithm will be measured for all subjects, by comparing both threshold values provided by the algorithm and by the Corelab at 1 and 3 months follow-ups. The estimated number of subjects to enroll is 170.

The primary outcomes are:

- The evaluation of the system-related complication-free rate.
- The evaluation of the accuracy of the LVAT Ambulatory test: comparison of threshold value of LVAT algorithm and a Corelab (independent physician). The accuracy of the algorithm will be measured for all subjects, at both 1 and 3 months follow-ups.

The secondary outcome is the evaluation of the percentage of LVAT commanded tests that result in an appropriate outcome. Test outcome would be inappropriate when LVAT threshold could not be determined due to a limitation of LVAT feature and might not occur in manual threshold tests.

The completion date of the study is expected to the end of year 2016.

d. Summary of literature from similar devices

Algorithm	**% of subjects with at least 1 test during a follow-up**	**% of complete* test**	**% successful** test versus manual test**	**% successful** test versus ECG**
Medtronic LVCM [10]			99.7% (+/- 1 step)	
Medtronic VectorExpress [7]	95%	78%	95% (+/- 2 steps)	
Boston scientific [14]	98%	89%	96% (+/- 2 steps)	99%

****A successful test means the threshold value provided by the algorithm is accurate.**

***A complete test means that the test was not aborted or interrupted.**

2.2.2. *SPOT (Spatial Projection of Tachycardia) clinical evaluation*

The SPOT clinical evaluation is a multicenter pilot study performed in France, between February, 29th 2012, and August 28th, 2013 that evaluated the reproducibility of SPOT curve. Spot curve is based on a morphologic

analysis of combination of endocardial electrograms that discriminates “capture” from “non capture” cardiac cycles. Subjects involved in the study have been followed until 3 months after implant, and until 1 year follow-up for the optional part. Results are detailed in the SPOT Clinical Study Report REP3694.

A part of the secondary objective was to compare the SPOT curves recorded with different LV pacing vectors, especially on cycle with a “capture” versus cycle without a “capture”. The aim of this study was to develop an algorithm capable to automatically identify the LV pacing threshold in the left ventricle. SPOT curves on each paced cycle were drawn and analyzed in order to distinguish capturing cycles from non capturing cycles.

A preliminary algorithm similar to the “In-Clinic LVAT” was elaborated based on data collected during the SPOT clinical evaluation, and the threshold value identified by the algorithm was compared to accurate value, provided by experts.

The algorithm was first optimized on a training data set (115 recordings from 22 subjects), and evaluated on a test data set (204 recordings from 22 subjects).

Evaluation of the LV pacing threshold with the SPOT method provided very promising results, as summarized in the following table.

	Training data	**Test data**
Accurate threshold	98% (113/115)*	99% (202/204)*

* No threshold was found for one subject’s test. The threshold was inaccurate for 3 tests.

The “In-Clinic LVAT” algorithm was implemented in the software of the Platinium CRT platform, encompassing some improvements (learning of SPOT study) and modifications (technical reasons) from the preliminary algorithm. For further details, see the Investigator Brochure (Appendix A).

This analysis was performed on IS1 leads only, meaning that additional LV pacing vectors available in an IS4 lead were not tested in this evaluation. For this reason, in the LEVEA study objectives, an analysis is duplicated: one analysis on common LV pacing vectors to IS1 and IS4 leads, and one analysis on all available LV pacing vectors.

2.3. RATIONALE

The new automatic pacing threshold test, proposed in this study and referred to the “In-Clinic LVAT” feature, is based on a morphologic analysis of a combination of endocardial electrograms. The ability of the endocardial signals combination to discriminate between capture and non capture beats have been demonstrated in a previous study (SPOT Clinical Study Report REP3694).

Following this first step, an algorithm has been developed to determine automatically the LV pacing threshold for all selected LV pacing vectors. The physician will therefore identify easily the LV pacing vector with the lowest pacing threshold.

However, this preliminary study was performed on IS1 leads only. IS4 LV pacing vectors have not yet been tested. Thus, the LEVEA study interest is:

- Assess the performance of the improved “In-Clinic LVAT” algorithm
- Analyze IS1 and IS4 leads common LV pacing vectors
- Analyze all available LV pacing vectors.

2.4. STATEMENT OF COMPLIANCE & ETHICAL PRINCIPLES

2.4.1. *Ethical consideration*

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice as described in ISO 14155, and the applicable regulatory requirement(s). This Clinical Investigation Plan (CIP) and informed consent forms will be submitted to the Ethics Committee (EC) for written approval. Any additional requirements imposed by the EC or regulatory authority (or Competent Authorities (CA) shall be followed. The Principal Investigator will assure that no planned deviation from the Clinical Investigation Plan (CIP) will take place except where necessary to eliminate an immediate hazard to the study participants. The Principal Investigator will promptly report to the EC and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

2.4.2. *Subjects insurance and potential compensation*

The civil liability of the sponsor and all its agents is underwritten by a policy taken out the sponsor with CHUBB. A copy of the insurance certificate is provided in Appendix C.

A dedicated insurance coverage, if required by local/country regulation, will be obtained by the Sponsor for a specific center or country.

2.4.3. *Confidentiality*

Confidentiality of subjects' data and identity will be maintained throughout the study and after.

All information and data sent to the sponsor concerning subjects or their participation in this study will be considered confidential by the sponsor. Only authorized personnel of the sponsor or a representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by the sponsor for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

2.4.4. *Property rights*

This CIP is property of the sponsor. It should not be altered, used or disclosed to a third party without prior written consent.

2.4.5. *Clinical trial results*

Clinical trial results will be communicated to appropriate authorities according to local laws after completion or termination of the study.

The study will be registered on the ClinicalTrials.gov website and updated on a regular basis.

3. **PURPOSE**

The purpose of the LEVEA study is to assess the performances of a new automatic LV pacing threshold test for bipolar and quadripolar LV leads when used by physicians during in-hospital follow-up.

This function is available on Platinium SonR CRT-D devices models 1811, 1841 and 1844, interrogated by a clinical programmer able to unlock the function during the clinical evaluation.

This "In-Clinic LVAT" feature is non CE-marked and is designed to be launched, under the supervision of a physician during subject follow-up.

3.1. PRIMARY OBJECTIVES

The primary objective of the study is to assess the success rate of LV threshold value identified automatically by "In-Clinic LVAT" feature compared to manual threshold test performed by physician.

3.2. SECONDARY OBJECTIVES

The secondary objectives are the following:

- Assessment of the diagnostic accuracy of the algorithm at M0 follow-up: Independent reviewer validation of the LV threshold value provided by algorithm.
- Assessment of the success rate of the algorithm at M0 follow-up: comparison to manual LV threshold tests results.
- Assessment of the success rate of the algorithm at M1 follow-up: comparison to manual LV threshold tests results.
- Evaluation of the applicability of the algorithm.
- Assess the device characteristics in terms of safety and deficiencies with a focus on "In-Clinic LVAT" feature.

3.3. ANCILLARY ANALYSIS

Right ventricular pacing electrograms might be collected and analyzed to identify right ventricular capture and non-capture beats and to assess a right ventricular threshold determination method on Platinium Implantable Cardioverter Device (ICD).

4. **CLINICAL INVESTIGATIONAL PLAN (CIP)**

4.1. STUDY DESIGN

This study is a prospective, comparative, non randomized, confirmatory study.

4.1.1. *Definition of LV Vector Test*

"In-Clinic LVAT" test is composed of several LV Vector Tests, each corresponding to a selected LV pacing vector.

The following definitions apply when performed on the same subject, with the same pulse width, on the same LV pacing vector and at the same follow-up:

- A complete LV Vector Test: test was performed (not aborted or interrupted) and a threshold value is provided by the algorithm.
- A successful LV Vector Test: threshold value provided automatically by the algorithm is equivalent to the manual threshold test done by the physician or adjudicated by the independent reviewer among the complete LV Vector Tests.
- A failed LV Vector Test: threshold value provided automatically by the algorithm is not equivalent to the manual threshold test done by the physician or adjudicated by the independent reviewer among the complete LV Vector Tests.

In case several LV Vector Tests were eligible with the same LV pacing vector, for the same subject, on the same follow-up, only the last one will be considered.

As values determined by the algorithm are not presented on the programmer screen, data will be stored in the technical analysis electronic files that will be sent to the sponsor in order to be extracted.

4.1.2. *Primary endpoint*

The primary endpoint of the study is the success rate of "In-Clinic LVAT" test.

The success is defined by a LV threshold value identified automatically by "In-Clinic LVAT" feature equivalent to the manual threshold test value performed by physician on at least 90% among complete tests (performance goal).

For the primary endpoint, the evaluation is performed on 5 LV pacing vectors common to IS1 and IS4 leads: LV bipolar, LVring-RVcoil, LVtip-can, LVtip-RVcoil, and LVring-can pacing vectors. Test will be evaluated at different pacing conditions: DDD A-test and VVI. Results will be analyzed irrespective of the type of lead used (bipolar or quadripolar) and in any test configuration (DDD A-test or VVI).

An equivalent LV threshold value is defined as the same value of automatic and manual LV threshold tests, with a flexibility of ± 2 steps (meaning ±0.5V if threshold<2.5V, else ±1V as measured in 2 consecutive cardiac cycles). A margin of ± 2 steps is accepted because of the variability of the threshold, and due to the design of the algorithm.

Among all the eligible complete LV Vector Tests collected, only those performed in DDD A-test with atrial overdrive pacing configuration (if available, otherwise in VVI) and with a manual LV threshold test performed in the same conditions and reported in the electronic Case Report Form (eCRF) will be retained. Only one LV Vector Test per LV pacing vector per subject will be analyzed.

In case several LV Vector Tests were eligible with the same LV pacing vector, for the same subject, on 2 different follow-ups, only M0 data will be considered.

The primary analysis is based on at least 231 complete LV Vector Tests provided by the algorithm and collected at M0. If data at M0 is unavailable, then corresponding data collected at M1 will be considered.

4.1.3. Secondary endpoints

a. *Assessment of the diagnostic accuracy of "In-Clinic LVAT" test at M0 follow-up: Independent reviewer validation of LV threshold value provided by algorithm*

This endpoint is the number of accurate determination of the pacing threshold value provided by the algorithm feature and an independent reviewer, on all LV pacing vectors and all pacing configurations available at M0 follow-up.

Diagnostic accuracy is defined as an adjudication of LV threshold value provided by the algorithm. The adjudication is based on capture and loss of capture analysis on electrogram strips recorded and stored during "In-Clinic LVAT" tests. The threshold value provided by the algorithm compared to the reviewer adjudication is considered accurate if the difference is within ± 1 step. The reason for incorrect determination of capture/loss of capture (if any) will be reported.

In case several LV Vector Tests were eligible with the same LV pacing vector, in the same pacing configuration, for the same subject, on the same follow-up, only the last one will be considered.

b. *Assessment of the success rate of "In-Clinic LVAT" test at M0 follow-up: comparison to manual LV threshold tests results*

This endpoint is the success rate of "In-Clinic LVAT" feature on pacing vectors and pacing configurations available at M0 follow-up. The method of analysis is similar to the primary endpoint.

c. *Assessment of the success rate of "In-Clinic LVAT" test at M1 follow-up: comparison to manual LV threshold tests results*

This endpoint is the success rate of "In-Clinic LVAT" feature on pacing vectors and pacing configurations available at M1 follow-up. The method of analysis is similar to the primary endpoint.

d. Evaluation of the applicability of the algorithm

The algorithm may not be applicable to some subjects, mainly because of a very long inter-ventricular conduction delay. A subject is defined as eligible as soon as one LV Vector Test is complete.

The endpoints for the applicability of the algorithm in the population are:

- The percentage of subjects who are eligible to receive the feature that is the percentage of subjects with at least one complete LV Vector Test at M0 and M1 follow-ups.
- The number of LV Vector Tests attempted, and percentage of completed and successful LV Vector Tests at M0 and M1 follow-ups per subject.

e. Assess the device characteristics in terms of safety and deficiencies

- Serious adverse device events and device deficiencies will be collected during each subject follow-up. Confirmation of absence of USADE during "In-Clinic LVAT" tests will be evaluated by analyzing all SAEs and device deficiencies collected at each follow-up.
- The focus of the "In-clinic LVAT" deficiencies will include:
    - Assessment of pacing threshold underestimation: comparison to manual LV threshold value will be performed by comparing manual and automatic LV threshold values at each follow-up. An underestimated LV threshold value of "In-Clinic LVAT" feature is defined as a value result more than 2 steps below the LV threshold measured manually. For all the eligible complete LV Vector Tests collected, only manual LV threshold test performed in the same conditions and reported in the electronic Case Report Form (eCRF) will be retained. Only one LV Vector Test per LV pacing vector per subject will be analyzed. In case several LV Vector Tests are eligible with the same LV pacing vector, for the same subject, on the same follow-up, only the last one will be considered.
    - Confirmation of absence of unexpected function operations by analyzing EGM and ECG performed during "In-Clinic LVAT" test at each follow-up. Any unexpected function operation will be reported.

4.1.4. *Ancillary endpoint*

Right ventricular pacing electrograms might be collected and analyzed to identify right ventricular capture and non-capture beats and to assess a right ventricular threshold determination method on Platinium Implantable Cardioverter Device (ICD).

4.2. NUMBER OF SUBJECTS/SITES

59 subjects should be included in approximately 12 sites in Europe.

4.3. STUDY DURATION

Each subject will participate in the study for maximum 3 months.

As the study plans an inclusion period of approximately 3 months, the study duration is approximately 6 months.

The Sponsor may perform adjustments/enhancements to the study CIP or eCRF as deemed appropriate in order to guarantee consistency to the main study endpoints. Whenever relevant and required, the EC and the Competent Authorities (CA) shall be notified by the investigator about any change made to the study.

4.4. INCLUSION CRITERIA

Subjects must meet all of the following criteria to be considered for enrollment:

- Subject already implanted (de-novo, upgrade or replacement) according to the relevant ESC Guidelines [1]:
    - With IS1 Platinium SonR CRT-D (models 1811, 1841, CE-marked) for maximum of 5 days or;
    - With IS4 Platinium SonR CRT-D (model 1844, CE-marked).
- Right atrial, right and left ventricular leads must be implanted. Only bipolar and quadripolar for Left Ventricular lead.
- Reviewed, signed and dated informed consent.

4.5. EXCLUSION CRITERIA

Subjects who meet any of the following criteria are not eligible to be enrolled in the study:

- Subject included in another clinical study that could confound the results of this study;
- Malfunction or dislodgment of right atrial, right and left ventricular implanted leads;
- Subject diagnosed with permanent atrial fibrillation;
- Known pregnancy;
- Minor age;
- Under protection or guardianship;
- Unavailability for scheduled follow-up or refusal to cooperate.

A subject will be considered eligible to be enrolled in the study when the Informed Consent has been completed and the subject satisfies all the inclusion and exclusion criteria. Individuals who are screened but do not satisfy the inclusion and exclusion criteria will not be considered enrolled in the study. Logs will be maintained for screening and consenting subjects.

5. INVESTIGATIONAL DEVICE INFORMATION

5.1. DEVICE DESCRIPTION

5.1.1. *Feature under investigation*

The feature under investigation is the “In-Clinic LVAT” Test.

It is a non CE-marked software function, embedded in Platinium SonR CRT-D devices and it is intended to be used only under medical supervision during subject follow-up by activating the function with dedicated clinical software of the programmer.

This featured is embedded in Platinium SonR CRT-D devices equipped with software version 2.4.2 (or upgraded version).

5.1.2. *Associated device not under investigation*

Platinium SonR CRT-D devices (models 1811, 1841, 1844) are triple chamber implantable cardioverter defibrillators CE-marked, designed to perform standard pacing and sensing functions.

The embedded software is CE-marked, similar to the commercial version with an unlocked non CE-marked function, the “In-Clinic LVAT” test.

The considered models are:

Platinium device	RV-LV leads		
	DF1-IS1	DF4-IS1	DF4-IS4
SonR CRT-D model	1811	1841	1844

5.1.3. *Implantable leads*

Any market approved right atrial (A) implantable lead, right ventricular (RV) cardioversion/defibrillation lead DF1 or DF4 and left ventricular (LV) implantable IS-1 or IS-4 lead (only bipolar and quadripolar) could be used as long as there is no malfunction and the leads integrity are preserved.

5.1.4. *Orchestra Plus Programmer*

In order to launch "In-Clinic LVAT" feature, an Orchestra plus programmer with the 2.54.C1 (or upgraded version) clinical SmartView version will be used.

This system is capable to launch:

- all available functions of the SmartView 2.54 commercial version (or upgraded version),
- "In-Clinic LVAT" tests.

5.2. DEVICE TRACEABILITY

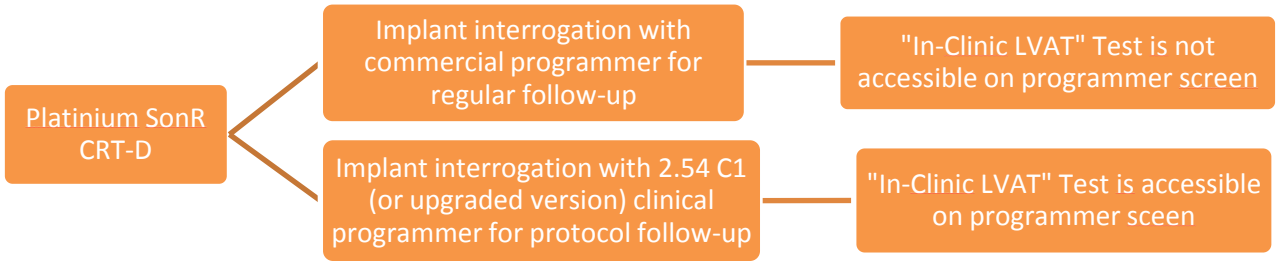
Devices will be used according to the physician's manual, to the clinical practice, and to the CIP.

To ensure traceability throughout the study, the serial number assigned to Platinium SonR CRT-D device, and the programmer will be documented in the device accountability log at the site level, with the following information:

- Subject identification Platinium SonR CRT-D model & serial number,
- Programmer serial number installed with 2.54 C1 software version (or upgraded version).

5.3. PURPOSE OF THE DEVICE

The "In-Clinic LVAT" test was designed to automatically determine the pacing threshold of a preselected set of LV pacing vectors in subjects implanted with a Platinium SonR CRT defibrillator. This feature is available only when the ICD (Platinium SonR CRT-D) is interrogated by a programmer (Orchestra Plus) equipped with a 2.54 C1 SmartView clinical version (or upgraded version). This function has no effect on the standard use of the CE-marked commercialized implant Platinium SonR CRT-D device.



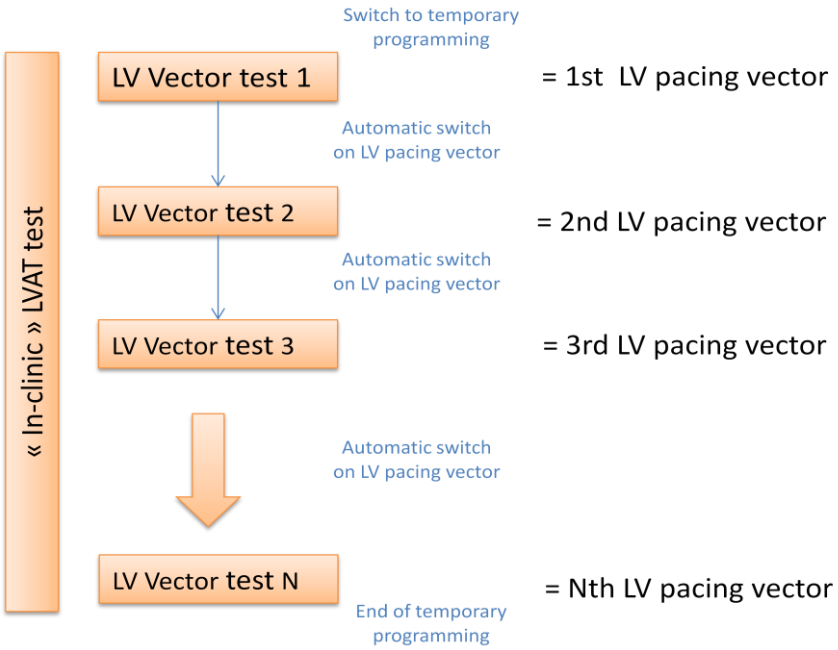
5.4. FEATURE USE

The “In-Clinic LVAT” function is capable to measure automatically the pacing threshold values of all LV pacing vectors selected by the physician, instead of a one by one manual test (as performed in routine practice). It is composed of several consecutive individual tests called LV Vector Tests.

Before launching this function, the physician needs to program a temporary configuration comprising of a pacing configuration, starting pacing amplitude, and pacing width.

Thereafter, all LV Vectors Tests are performed sequentially. More precisely, the LV Vector Test 1 starts by launching the function and decrementing automatically the LV pacing amplitude, in order to determine the threshold value. In turn, the following LV Vector Test is automatically launched by modifying automatically the LV pacing vector programming, and so on until the last LV Vector Test. All these steps are performed automatically, and results are displayed on the programmer screen to be exploited by the physician.

Flowchart of test functioning:



“In-Clinic LVAT” tests are detailed in the Investigator Brochure (Appendix A).

6. STUDY PROCEDURES

Prior to investigational site activation or involvement in study activities, all personnel participating in the study must be trained on the investigational feature, the CIP and the study-specific electronic data capture (EDC) system. It may also include GCP training, if necessary, and can only be provided by dedicated and experienced staff (sponsor or sponsor delegated staff). All study-specific trainings will be documented and filed at both site and sponsor level.

The study feature should be used in accordance with the corresponding Instructions For Use (IFU) (MISC3606).

Detailed guidelines on data to be recorded for the study, and how to fill in the eCRFs in the EDC system will be provided to the Investigators.

6.1. TREATMENT AND EVALUATION

6.1.1. *Inclusion follow-up*

Subjects must be informed about the investigation and the potential benefits and risks of the study prior to enrollment. Only those subjects who voluntarily provide written consent to participate will be eligible for enrollment.

The following procedures must be conducted before inclusion of the subject in the study:

- Evaluate subject eligibility based on the inclusion and exclusion criteria
- Obtain written informed consent
- Source data that demonstrate conformance with inclusion criteria should be retained at the investigational site

The following procedures must be conducted in order to include the subject in the study:

- Report implant information
- Report subject's medical history
- Report subject's clinical examination including current vital signs and NYHA classification
- Report subject's current concomitant medications (based on the EDC questions)

6.1.2. *M0 follow-up*

- Perform a complete interrogation of the device with the appropriate clinical programmer
- Print report file
- Measure P-R, A-R and V-V inter ventricular conduction durations on the EGM
- Launch manual LV threshold tests on:
  - 5 common LV vectors to IS1 and IS4 for all subjects,
  - 4 dedicated IS4 LV vectors for subject implanted with IS4 LV lead (LV2-LV4, LV3-LV4, LV3-LV2, LVtip1-LV4).

Manual tests should be performed prior to automatic test to limit bias.

Optional manual threshold tests on additional LV pacing vectors could be performed under physician discretion.

- ECG record:
  - Spontaneous rhythm,
  - Paced rhythm during "In-Clinic LVAT" test in DDD A-test for 30 seconds recording corresponding to 10 seconds before launching test and 20 seconds during the test.
- Launch "In-Clinic LVAT" test on all LV pacing vectors in following pacing configuration:
  - DDD A-test
  - DDD P-test
  - VVI
- Perform right ventricular pacing recordings data collection using RF telemetry to allow collection of multiple EGM:
  - RV A-test

- RV P-test

- Retrieve subject technical data analysis files
- Report Adverse Events and Serious Adverse Events occurred during the testing procedure if any
- Report Device Deficiencies if any

6.1.3. M1 follow-up

- Perform a complete interrogation of the device with the appropriate clinical programmer
- Print report file
- Measure P-R, A-R and V-V inter ventricular conduction durations on the EGM
- Launch manual LV threshold tests on:
  - 5 common LV vectors to IS1 and IS4 for all subjects,
  - 4 dedicated IS4 LV pacing vectors for subject implanted with IS4 LV lead (LV3-can, LV3-RVring, LV3-RVcoil, LV4-RVcoil).

Manual tests should be performed prior to automatic test to limit bias.

Optional manual threshold tests on additional LV pacing vectors could be performed under physician discretion.

- ECG record:
  - Spontaneous rhythm,
  - Paced rhythm during "In-Clinic LVAT" in DDD A-test for 30 seconds recording corresponding to 10 seconds before launching test and 20 seconds during the test.
- Launch "In-Clinic LVAT" test on all LV pacing vectors in following pacing configuration:
  - DDD A-test
  - DDD P-test
  - VVI
- Perform right ventricular pacing recordings data collection using RF telemetry to allow collection of multiple EGM:
  - RV A-test
  - RV P-test
- Retrieve subject technical data analysis files
- Report Adverse Events and Serious Adverse Events occurred during the testing procedure if any
- Report Device Deficiencies if any
- Report Serious Cardiovascular Adverse Event occurred since last follow-up if any

6.1.4. *Unscheduled follow-ups*

If the subject comes in due to a serious cardiovascular adverse event, re-intervention, or if the subject's device is interrogated for any reason outside of regular follow-up, the routine follow-up procedure should be performed when possible.

6.2. STUDY CONCLUSION

All study and printout reports should be on document and retrieved on the subject's medical file.

Next subject follow-up will be scheduled by the physician according to his/her standard clinical practice.

Study completion for a subject will occur after he/she has completed M1 follow-up.

6.3. PREMATURE SUBJECT WITHDRAWAL OR DISCONTINUATION

For subjects lost to follow-up, the Principal Investigator must ensure all reasonable efforts have been made to contact the subject to return for a CIP-required follow-up. These efforts shall be documented. It is expected that the Principal Investigator and site personnel will act in an ethical manner to encourage each subject to complete the study.

For subjects discontinued by the Principal Investigator for safety reason, the Principal Investigator shall document the reasons for his/her decision.

6.4. SUBJECT STUDY TERMINATION RECORD

A study termination record must be completed and signed by the Principal Investigator for each subject enrolled in the study. The study termination record will capture the reason for study termination (e.g. early termination, lost to follow-up, study completion).

7. **RISK ANALYSIS**

7.1. POTENTIAL & RESIDUAL RISKS

The risk analysis and the risk mitigation of the investigational feature are detailed in the Investigator Brochure (Appendix A). The main risks include the following:

- Anodic stimulation or fusion leading to under-estimation of the pacing threshold
- Inappropriate or absence of back up pacing leading to long ventricular cycle
- Slow VT detection temporarily turned off during the test leading to inability to detect Slow VT during the test

These risks are all mitigated by design and are considered acceptable.

The Global Product Analysis of the device supporting the feature under investigation (Ref. AR00523 and AR 00503) did not identify any significant additional risk related to device use.

The procedures required by the CIP do not differ from routine follow-up practice, except for the launch of the "In-Clinic LVAT" tests which is not expected to lead to other risks that the ones associated to standard threshold pacing tests.

7.2. POTENTIAL BENEFITS

Platinium SonR CRT-D implant offers the same potential clinical benefits for subject as any commercial CRT implantable defibrillator.

However, subjects who are participating to the study will not have direct benefits from the clinical evaluation, although they will have a comprehensive assessment of electrical performances of their left ventricular lead. Nevertheless, once marketed, this automatic tool will allow physician to identify and program the optimal configuration of subject device in a timely manner.

7.3. MITIGATION

To protect the welfare of subjects, ethics committee and/or competent authority approval of the investigation will be obtained for each site prior to the first implant at that site.

Investigators selected to participate in this study will have experience in the follow-ups of CRT-D systems. Trained and experienced LivaNova representatives will be made available to support follow-ups and in case of troubleshooting.

Training will be provided to the investigators and their staff to ensure that the CIP and study procedures and instructions to be performed are understood and will be applied.

Each investigator will sign an Investigator Agreement stating his/her responsibility to conduct this study according to this investigational plan, to adhere to the records and reporting requirements, and to supervise use of the investigational device.

Through careful design and testing, LivaNova has attempted to minimize the risk to subjects. Testing included bench testing or device performance and software validation testing.

Risks can be minimized through compliance with the CIP, using the devices in accordance with their applicable Instructions for Use, performing the procedures following recommended standard practices/guidelines, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's status and by promptly supplying the Sponsor with all pertinent information required by this CIP.

7.4. RISK-TO-BENEFIT ANALYSIS

The Sponsor believes that the value of the knowledge to be gained by conducting this clinical study to evaluate LEVEA outweighs the potential risks posed to the participating subjects. There is no anticipated increased risk related to the participation in the study.

8. STATISTICAL CONSIDERATIONS

The statistical analysis will be performed as mentioned in this CIP and detailed in the Statistical Analysis Plan (SAP). Endpoints and time points are described in the other CIP sections.

Any relevant major change to the statistical analysis requested after CIP approval must be defined and approved through a CIP amendment or must be clearly mentioned in the statistical plan of the study in a section 'Changes in the conduct of analyses from CIP', including the rationale of changes.

8.1. SAMPLE SIZE CALCULATION

The study primary objective will be met in case the null hypothesis that the success rate of the "In-Clinic LVAT" is at least than 90% is be rejected.

The statistical analysis of primary endpoint will be performed on the ITT population (see section 8.2).

A sample size of at least 231 evaluable LV pacing vectors (configuration) will provide 80% power to reject the trial null hypothesis by using a one-sided alpha 2.5% and assuming an expected success rate of 95% – configuration based. As each subject can provide data on 5 different pacing vectors, 47 (~231/5) subjects are needed for the statistical analysis. Accounting for a global attrition rate of 20%, 59 subjects shall be enrolled.

8.2. ANALYSIS POPULATION

The analysis populations will be reviewed and determined during the Data Review meeting based on all included subjects. The included population will consist of all subjects who have completed "Inclusion Form".

The main analysis populations are:

- The Intention To Treat (ITT) population will consist of all included subjects with at least 1 eligible complete LV Vector Tests at M0 follow-up (if unavailable, M1 follow-up will be considered). This population will be used for the assessment of the primary endpoint (see section 4.1.2).
- The M0-Intention To Treat (M0-ITT) population will consist of all included subjects with at least 1 eligible complete LV Vector Tests at M0 follow-up. This population will be used for the assessment of the secondary endpoints concerning the LV test done at M0 follow-up (see section 4.1.3).
- The M1-Intention To Treat (M1-ITT) population will consist of all included subjects with at least 1 eligible complete LV Vector Tests at M1 follow-up. This population will be used for the assessment of the secondary endpoints concerning the LV test done at M1 follow-up (see section 4.1.3).
- The included population will be used for the assessment of the secondary endpoint "Applicability of the algorithm" (see section 4.1.3).
- The safety population will consist of all subjects included and implanted with Platinium SonR CRT-D 1811, 1841 or 1844.The number of subjects in each population will be mentioned in the disposition of subjects.
- Ancillary population will consist of all included subjects with at least one right ventricular pacing electrogram collected during RV A-test or RV P-test at M0 or/and M1 follow-up (see section 4.1.4).

8.3. GENERAL STATISTICAL CONSIDERATIONS

According to the type of parameters, the summary results will be presented at least as follows:

- Continuous parameters: number and percentage of subjects with available and missing data, mean, standard deviation (SD), median, quartiles (Q1, Q3), and the extreme values (Minimum; Maximum).
- Categorical and ordinal data: number and percentage of subjects. For some specific categorical data as adverse events, number of events and the number of subjects having at least one event (morbidity or mortality) will be presented. In case of ordinal parameter, descriptive statistics will be performed as a quantitative parameter if relevant.

8.4. DEMOGRAPHICS AND SUBJECT CHARACTERISTICS

Description of subjects, including subjects' characteristics and medical history will be summarized to describe the study population.

8.5. ANALYSIS OF PRIMARY, SECONDARY AND ANCILLARY ENDPOINTS

8.5.1. *Primary endpoint*

The trial null hypothesis is that the success rate of the "In-Clinic LVAT" feature is lower than 90%. The alternative hypothesis is that the success rate of the "In-Clinic LVAT" feature is at greater than or equal to 90%.

The Primary endpoint is discussed in details in Section 4.1.2.

A one-sided exact binomial test for proportion at 2.5% level of significance (alpha) will be performed to test the null hypothesis for the primary endpoint. The null hypothesis will be rejected if the p-value is less than 0.025.

Handling of Missing values/censoring/Discontinuations

The primary endpoint will primarily be based on the completed LV Vector Tests provided by the algorithm and collected at M0. If data at M0 is unavailable, then corresponding data collected at M1 will be considered. If data at both M0 and M1 is missing, no imputation will be done.

Supportive Analysis of the Primary Endpoint

i. The estimate of the success rate will be presented along with exact 95% confidence interval (CI) (Clopper & Pearson, 1934). [2]

ii. Bayesian analysis will be performed to calculate the probability that the success rate is greater than or equal to 90%. A non-informative prior for the success rate (~Beta (1, 1)) will be assumed. Thus, if x successes out of n completed LV vector tests is observed, then success rate will have a posterior distribution Beta(x+1,n-x+1). A 95% credible interval will also be calculated for the success rate.

8.5.2. *Secondary and ancillary endpoints*

Secondary and ancillary endpoints will be assessed at all follow-ups using descriptive statistics. Point estimates and 95% CI will be presented wherever possible.

8.6. SAFETY ANALYSIS

The secondary objective of assessing safety and device deficiencies of the compound will be answered by summarizing the relevant endpoints by means of descriptive statistics on the Safety population.

9. **DATA MANAGEMENT**

9.1. CASE REPORT FORMS (CRFS), DATA REVIEW, DATABASE CLEANING, ISSUING AND RESOLVING QUERIES

The Principal Investigator and authorized site personnel must enter the information required by the CIP on the eCRF. Data are to be entered into a clinical database as specified in the Data Management Plan (DMP). Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

The Principal Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto electronic CRFs (eCRFs) from an Electronic Data Capture (EDC) system developed by the EDC vendor. All CIP-required data, unless otherwise specified, will be recorded on eCRFs or, if requested, provided in an electronic format (e.g., device settings data). All eCRFs and electronic data must be handled in accordance with instructions from the Sponsor and submitted to the Sponsor in a timely fashion. At the end of the study, the Principal Investigator may request a copy of the eCRFs. All data will have separate source documentation; no data will be recorded solely onto the eCRF.

All CRF data sent to the Sponsor must be endorsed by the Principal Investigator.

Data will be reviewed according to the Data Management Plan (DMP) in order to perform the database cleaning. Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. In case of inconsistencies, inaccurate data or other discrepancies, data queries will be generated for those data points requiring clarification from the site.

After resolution of all inconsistencies and discrepancies, a global data review will be performed in order to prepare the final study database. The final locked database will be provided for the statistical analysis.

9.2. VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEM

Study data will be entered into a Clinical Data Management System (CDMS) as specified in the Data Management Plan (DMP). The software used for data management should be reliable, and documentation of appropriate software testing procedures should be available. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database. Access to the study data will only be given to authorized and trained users, and all corrections are documented in an auditable manner.

10. SAFETY REPORTING

The Sponsor is responsible for the ongoing safety evaluation of the investigational device, review of reported adverse events (AE), investigation of Unanticipated Serious Adverse Device Effects (USADE), and notification of regulatory authorities per applicable requirements. The Sponsor is also responsible for training the investigational staff prior to start the study on any study-related procedures, including reporting of Serious Adverse Events (SAE).

The Sponsor, through the Clinical Safety Office, will provide oversight of general AE handling procedures for the clinical study and can assist the investigators and various committees in conducting a medical review of reported serious adverse events.

The Principal Investigator is responsible for ensuring the safety and well-being of the subjects enrolled in their clinical sites and should report events to the Sponsor, Ethics Committees, and regulatory bodies as described in this section.

10.1. DEFINITIONS

Adverse events definitions are derived from ISO 14155:2011 - Clinical investigation of medical devices for human subjects. The definitions of the following terms can be found in the glossary (section 14):

- Adverse Event – AE
- Adverse Device Effect – ADE
- Device deficiencies
- Serious Adverse Event – SAE
- Serious Adverse Device Effect - SADE
- Unanticipated Serious Adverse Device Effect –USADE

10.2. PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES IN ADVERSE EVENT REPORTING

The responsibilities of the principal investigator include the following:

- The Principal Investigator is required to report the following adverse events to the Sponsor:
  - Unanticipated Serious Adverse Device Effects should be reported to the Sponsor within 24 hours of awareness of the event by notifying the Sponsor Clinical Project Manager and by entering the information in the EDC. These events require urgent investigation by the Sponsor and reporting to regulatory authorities, as applicable.
  - All adverse events (serious and non-serious) during the testing procedure should be reported. However, conditions that occur due to direct physiologic effects of testing (e.g. PNS, palpitations, and discomfort) are not considered adverse events.
  - Serious cardiovascular and access site adverse events from inclusion (signing date of inform consent) to termination should be reported as soon as possible but no later than 3 calendar days upon awareness. The Principal Investigator should enter all available information in the "AE section" of the EDC system. Cardiovascular events refer to those that are classified under cardiac disorders, bleeding disorders, cerebrovascular, and peripheral vascular as defined in the trial-specific AE classifications (Appendix B).
  - Device deficiencies should be reported within 5 calendar days of awareness. Deficiencies of the Sponsor study device should be reported in the Device Deficiencies section in EDC. The Principal Investigator must return the device, if possible, to the Sponsor. Deficiencies of the non-Sponsor study device should be reported following the commercial reporting procedure for that device.

Timelines and Communication Methods for Reporting Adverse Events

Study Period	Event Classification	Communication Method	Communication Timeline
During initial testing procedure	All adverse events e.g. procedural complications (serious and non-serious), excluding direct physiologic effects of testing	Complete AE eCRF page with all available information.	Within 3 calendar days of first becoming aware of the event
Throughout study duration	All Serious cardiovascular and access site Adverse Events	Complete AE eCRF page with all available information.	Within 3 calendar days of first becoming aware of the event
Throughout study duration	All deaths	Complete AE eCRF page with all available information. Provide all relevant source documentation (unidentified) for reported event	Within 1 business day of first becoming aware of the event.
Throughout study duration	Unanticipated (Serious) Adverse Device Effect	Complete AE eCRF page with all available information. Provide all relevant source documentation (unidentified) for reported event	Within 1 business day of first becoming aware of the event. Reporting of any updated information required through the end of the study
Throughout study duration	Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) with or without associated adverse events	Complete Device Deficiency eCRF with all available new and updated information	Within 5 days first becoming aware of the event and as per local/regional regulations Reporting required through the end of the study

- The Principal Investigator should perform the following assessments for each reported serious adverse event:
  - Identify the clinical event (Diagnosis or symptoms),
  - Seriousness of the event,
  - Relationship of the event to the device and/or procedure.
- The Principal Investigator should provide all the information needed to complete the AE electronic CRF.

- The Principal Investigator is responsible for informing the Ethics Committee, and regulatory authorities of serious adverse events as required by local/regional regulations.
- The Principal Investigator is expected to assist in clinical review and supply the Sponsor with relevant source documents and results of ancillary procedures required in the CIP.

10.3. SPONSOR REPORTING RESPONSIBILITIES

The Sponsor is responsible for reporting serious adverse event information to all participating investigators, ECs and regulatory authorities, as applicable following local regulations. USADE investigation results will be reported to the competent authorities all ECs and all participating investigators within 10 working days of the Sponsor's first notice of the effect. The Sponsor will also notify the competent authorities, all ECs, and all participating investigators of any EC withdrawal of approval within 5 working days of receipt of the approval withdrawal.

If the Sponsor determines an USADE to be an unreasonable risk to subjects, all parts of the investigation presenting that risk will be terminated or suspended as soon as possible, no later than 5 working days after said termination and no later than 15 working days after the Sponsor' first notice of the USADE. All SAEs must be reported to EC following the EC's safety reporting guidelines. The suspended study may not resume until the study has received both EC and FDA approval.

10.4. CONTACT DETAILS FOR REPORTING SERIOUS ADVERSE EVENTS AND SERIOUS ADVERSE DEVICE EFFECTS

In case of questions for reporting of adverse events, please contact the Clinical Project Manager of the study or the Monitor responsible for your site.

11. INDEPENDENT CLINICAL STUDY COMMITTEES: INDEPENDENT REVIEWER

An independent physician will review and adjudicate technical data of the LV pacing threshold value provided by the algorithm.

12. ADMINISTRATIVE REQUIREMENTS

12.1. ETHICS COMMITTEE (EC)

Subject inclusion cannot start before written approval of Ethics Committee (EC) of the CIP and the informed consent.

The Principal Investigator must report to the Sponsor withdrawal of EC approval within 5 working days. This study will be managed in accordance and full compliance with recognized Good Clinical Practices (ISO14155).

12.2. INFORMED CONSENT PROCESS

The investigational site must obtain written informed consent from each subject before any study procedures or evaluations are obtained. The informed consent form must be approved by the Sponsor prior to EC submission and by the EC prior to subject enrollment.

Subject information and consent contain all relevant aspects pertaining to the clinical investigation in writing and in native, non-technical and understandable language.

Subject's informed consent must be obtained and documented according to the principles of informed consent in the current version of the Declaration of Helsinki for Protection of Human Subjects, ISO 14155, and any local regulations, as applicable.

Failure to obtain subject consent needs to be reported to the applicable regulatory authority according to their requirements by either the site or the Sponsor.

Process for obtaining informed consent

Prior to inclusion, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator or designee. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the study. Subject must be given ample time and opportunity to inquire about details of the study and all questions about the study should be answered to the satisfaction of the subject.

Prior to inclusion, where applicable per local regulation, the written informed consent form should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (Investigator or designee). If the subject is unable to read the consent form, a witness should be present during the entire informed consent discussion. After the informed consent is read to the subject and signed by the subject, the witness should also sign the consent form, attesting the subject freely gave that informed consent.

The subject must receive a copy of the signed and dated informed consent.

The consent form that is to be used must be approved by both the reviewing Ethics Committee and by the Sponsor.

Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities, as appropriate.

12.3. CURRICULUM VITAE

Study investigators will provide updated curriculum vitae with current position and evidence of required qualifications through education, training and experience.

12.4. SITE QUALIFICATION

Prior to initiation, site will be qualified and must fulfill the following criteria:

- have the capability to include at least 6 subjects in 3 months
- equipped for electronic data capture
- equipped with radiofrequency system telemetry (RF)
- has a dedicated study nurse
- Platinium SonR CRT-D model 1844 is available on the hospital market
- possibility to implant Platinium SonR CRT-D model 1844 with any available market approved IS4 lead

The final list of participating investigators and sites is maintained by the Sponsor and will be published in the final study report.

12.5. STUDY INITIATION

During site initiation, all participants involved in the study will be trained on:

- CIP
- GCP
- Specific technical requirements for the study
- Specific study reporting

A site training log will be documented for each participant, maintained updated on site file. A copy will be archived on sponsor site file.

12.6. CIP ADHERENCE/ CIP AMENDMENT

The Principal Investigator must conduct the study as described in this CIP except for an emergency situation in which proper care of the subject requires immediate action. Any such deviation from the CIP must be reported promptly to the Sponsor. Deviations affecting subject's safety and/or well-being will be promptly reported to EC and competent authorities, if applicable. Any deviation from the investigational plan to protect life or physical well-being of a subject in an emergency shall be reported within 5 days to the sites EC and the Sponsor.

Deviations are defined as changes in the conduct of the study from that specified in the CIP that compromise the subject's rights, safety, or well-being, or the completeness, accuracy, reliability or scientific integrity of the study data.

In case of deviation, site must be trained on CIP and /or GCP.

Any significant change to the CIP requires an amendment. The Sponsor will originate any amendment that is deemed necessary and will include a summary of changes with the submission documents to the EC. All amendments must be approved by the EC before being implemented. If a CIP amendment has an impact on the informed consent process, the informed consent form must be revised. The revised consent forms must be approved by the EC. Each active study subject must sign the EC-approved, revised consent form to continue in the study when required by the EC. The Principal Investigator will not conduct any "add-on" studies or research on the subjects actively participating in this study without the express written approval of the Sponsor.

12.7. STUDY MATERIAL

The study material is "In-Clinic LVAT" feature. This function is available only when the implantable defibrillator (Platinium SonR CRT-D) is interrogated by a programmer (Orchestra Plus) equipped with a 2.54 C1 SmartView clinical version (or upgraded version).

Subject data will be reported on the study eCRF.

12.8. MONITORING PROCEDURES, AUDITS AND INSPECTIONS

Monitoring of the clinical study will be an interactive process overseen by the Sponsor monitoring team to ensure that high-quality data is obtained and that the study is conducted in compliance with the CIP, investigator agreement, applicable laws, regulations, and good clinical practice as established in the sponsor's monitoring plan.

Appropriately trained personnel designated by the Sponsor will monitor subject data at the investigative site.

In addition, the Sponsor may conduct a quality audit of the study for quality assurance. Other inspections by regulatory authorities may include on-site inspections and source data verification. The Principal Investigator will notify the Sponsor immediately in case of an inspection notification at the investigational site. It is important that the Principal Investigator and relevant study staff are available during the monitoring follow-ups, audits and inspections and that sufficient time is devoted to the process.

12.9. ROLE OF SPONSOR REPRESENTATIVES

Sponsor personnel can provide technical support to the Principal Investigator as needed during the study, testing required by the CIP, follow-ups, and on-site troubleshooting if necessary. Support may include Investigative site training, addressing questions, or providing clarifications to investigative sites concerning the operation of the Sponsor's equipment/devices (including programmers and other support equipment).

Under investigator supervision, Sponsor personnel may operate ”In-Clinic LVAT” feature assist with the conduct of testing specified in the CIP, and interact with the subject to accomplish requested activities. Typical tasks may include the following:

- Demonstrate the assembly and operation of ”In-Clinic LVAT” feature
- Clarifying device behavior, operation or output as requested by the Principal Investigator
- Assisting with the collection of study data from “In-Clinic LVAT” feature and other equipment as required by CIP
- In addition, Sponsor personnel may perform certain activities to ensure study quality. These activities may include the following:
- Observing testing or medical procedures to provide information relevant to CIP compliance
- Reviewing collected data and study documentation for completeness and accuracy
- On-site troubleshooting if necessary

Sponsor personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject’s condition or treatment with a subject without the approval and presence of the Principal Investigator
- Independently collect critical study data (defined as safety or effectiveness endpoint data)
- Enter data in the investigative site electronic data capture systems or on paper case report forms

12.10. STUDY SITE TERMINATION OR SUSPENSION

The Sponsor may terminate or suspend the entire study or a specific site’s participation at any time for any of the following reasons: inadequate enrollment, CIP non-adherence, unethical practices, poor data quality, or administrative decision. Subject included in the study will be followed as hospital standard practice.

12.11. INVESTIGATOR REPORTS

The Principal Investigator must provide the following reports to a Sponsor designee in a timely manner (for safety reports, refer to 14)

Investigator Reporting Requirements

Report Type	**Timeframe for Reporting**	**Report to:**
Withdrawal of EC approval	5 Working Days	Sponsor
Other reports	Upon Request	Sponsor, FDA, EC, and/ or other regulatory agencies

12.12. DATA RETENTION

12.12.1. *Investigator*

The Principal Investigator must retain all study records, including a copy of the CRFs according to country specific regulatory requirements after the later of the date the study is terminated or completed or that

records are no longer required to support a pre-market approval application. The Principal Investigator shall contact the Sponsor for authorization prior to destroying any study records. Data will be retained at least 15 years after study closure, starting from the signature date of the study report.

12.12.2. *Sponsor*

Study-related documentation in paper format will be organized, maintained and archived to manage the study in dedicated paper binder (Trial Master File, Country File, Sponsor Site File and Investigator Site File). Throughout the study and after, measures will be taken to prevent accidental or premature destruction of study documentation. Electronic data will be stored on the Sponsor servers.

Raw data will be stored on the EDC provider servers. Study case report forms, data clarification forms, and other supports, will be filed and archived at the Principal Investigator and Sponsor sites. Data will be retained at least 15 years after study closure, starting from the signature date of the study report.

13. PUBLICATION POLICY

Study results will be pooled across all sites participating in the study for the purpose of preparing a single, multi-site publication that will be coordinated by the Sponsor. Preparation of the comprehensive publication will occur at study end, but the Sponsor may, at its discretion, coordinate an additional, interim publication. The order of authorship will be determined by the Sponsor and will be based in part on the number of CIP compliant subjects at each site. Only the Principal Investigator for sites with high quality data will be considered for participation as an author.

Individual publication has to wait until primary objective of the study has been published.

An investigator intending to publish results of the study must provide the Sponsor with a copy of any proposed publication, abstract, or presentation at least 60 days prior to submission for publication or presentation. The Sponsor shall have the right to object to the publication, abstract, or presentation if in the Sponsor's reasonable opinion such publication (i) contains Confidential Information; or (ii) will adversely affect any intellectual property or proprietary right of the Sponsor. In the event of an objection by the Sponsor the Principal Investigator must either modify or delay the publication, abstract, or presentation for a period requested by the Sponsor not to exceed ninety to one hundred-twenty (90 to 120) days to permit the Sponsor to protect its interests.

14. DEFINITIONS, GLOSSARY AND ABBREVIATIONS

- **Adverse Device Effect (ADE):** adverse event related to the use of an investigational medical device.

  NOTE 1: this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

  NOTE 2: this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

- **Adverse Event (AE):** any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

  NOTE 1: this definition includes events related to the investigational medical device or the comparator.

  NOTE 2: this definition includes events related to the procedures involved.

  NOTE 3: for users or other persons, this definition is restricted to events related to investigational medical devices.

- **Device Deficiency:** inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

  NOTE: device deficiencies include malfunctions, use errors and inadequate labeling.

- **EC (Ethics Committee):** independent body whose responsibility is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation.

  NOTE: also known as Institutional Review Board (IRB), Research Ethics Committee and Independent Ethics Committee.

- **Major Adverse Cardiac and Cerebrovascular Event (MACCE):** Composite of key cardiovascular events such as deaths, myocardial infarction, stroke, and re-interventions. The specific components are defined in the Clinical Investigation Plan.

- **Malfunction:** failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

- **Principal Investigator (PI):** qualified person responsible for conducting the clinical investigation at an investigation site.

  NOTE 1: if a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

  NOTE 2: whether this is the responsibility of an individual or an institution can depend on national regulations.

- **Serious Adverse Device Effect (SADE):** adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

- **Serious Adverse Event (SAE):** adverse event that

  a. led to death.
  b. led to serious deterioration in the health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-subject or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  c. led to foetal distress, foetal death or a congenital abnormality or birth defect.

  NOTE: planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

- **Unanticipated (Serious) Adverse Device Effect (UADE/USADE):** serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

  NOTE 1: anticipated serious adverse device effect (ASADE) is a serious device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

  NOTE 2: UADE (FDA term) and USADE (ISO term) share the same definition.

- **Use error:** act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

  NOTE 1: use error includes slips, lapses and mistakes.

  NOTE 2: an unexpected physiological response of the subject does not in itself constitute a use error.

List of abbreviations:

ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy on a defibrillator
DF1	Standard for connection of defibrillator leads described in the ISO 11318:2002
DF4	Standard for connection of RV tachy leads described in the ISO 27186
DMP	Data Management Plan
EC	Ethic Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGM	Electrogram
ESC	European Society of Cardiology
GCP	Good clinical practice
ICD	Implantable Cardioverter Defibrillator
IFU	Instruction For Use
In-Clinic LVAT	In-clinic Left Ventricular Auto-Threshold
IS1	Standard for connection of pacing/sensing leads described in the ISO 5841-3:2013
IS4	Standard for connection of LV CRT leads described in the ISO 27186
ITT	Intention To Treat
LV	Left Ventricle
LVCM	Left Ventricular Capture Management
LVAT	Left Ventricular Auto Threshold

M0-ITT	M0- Intention To Treat
M1-ITT	M1- Intention To Treat
PI	Principal Investigator
PNS	Phrenic Nerve Stimulation
RF	Radiofrequency
RV	Right Ventricle
RVAT	Right Ventricular Auto Threshold
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPOT	Spatial Projection of Tachycardia
USADE	Unanticipated Serious Adverse Device Effect

15. REFERENCES

The following articles were referenced in this CIP.

List of bibliographic references pertaining to clinical investigation:

1. McMurray, J.J.V., et al., *ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012.* European Heart Journal, 2012. **33**(14): p. 1787-1847.
2. Clopper, C.J. and E.S. Pearson, *The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial.* Biometrika, 1934. **26**(4): p. 404-413.
3. Crossley, G.H., et al., *Performance of a novel left ventricular lead with short bipolar spacing for cardiac resynchronization therapy: Primary results of the Attain Performa Quadripolar Left Ventricular Lead Study.* Heart Rhythm, 2015. **12**(4): p. 751-758.
4. Philippon, F., et al., *A novel quad-polar LV lead providong two zone pacing*, in *Europace*. 2012. p. i57:176P_26.
5. Prévot, S., et al., *Quad-polar lead provides reliable LV mid and basal pacing*, in *Europace*. 2012. p. i57: 176P_16.
6. Forleo, G.B., et al., *Left ventricular pacing with a new quadripolar transvenous lead for CRT: Early results of a prospective comparison with conventional implant outcomes.* Heart Rhythm, 2011. **8**(1): p. 31-37.
7. Johnson, B., *Accuracy of an Automated Pacing Capture Thresholds Algorithm for Quadripolar Left Ventricular Leads.*, in *Heart Rhythm*. 2014.

8. Klein, N., et al., *Clinical efficacy of left ventricular pacing vector programmability in cardiac resynchronization therapy defibrillator patients for management of phrenic nerve stimulation and/or elevated left ventricular pacing thresholds: insights from the Efface Phrenic Stim study.* Europace, 2012. **14**(6): p. 826-832.

9. Pierantozzi, A., et al., *Automatic adjustment of stimulation output in resynchronization therapy: impact and effectiveness in clinical practice.* Europace, 2011. **13**(9): p. 1311-1318.

10. Crossley, G.H., et al., *Automated Left Ventricular Capture Management.* Pacing and Clinical Electrophysiology, 2007. **30**(10): p. 1190-1200.

11. Murgatroyd, F.D., et al., *Manual vs. automatic capture management in implantable cardioverter defibrillators and cardiac resynchronization therapy defibrillators.* Europace, 2010. **12**(6): p. 811-816.

12. Burri, H., et al., *Fluctuation of left ventricular thresholds and required safety margin for left ventricular pacing with cardiac resynchronization therapy.* Europace, 2009. **11**(7): p. 931-936.

13. Biffi, M., et al., *Automatic Management of Left Ventricular Stimulation: Hints for Technologic Improvement.* Pacing and Clinical Electrophysiology, 2009. **32**(3): p. 346-353.

14. Kalahasty, G., et al., *Acute Clinical Evaluation of a Left Ventricular Automatic Threshold Determination Algorithm Based on Evoked Response Sensing.* Pacing and Clinical Electrophysiology, 2012. **35**(3): p. 348-356.

16. **APPENDICES**

16.1. APPENDIX A: INVESTIGATOR'S BROCHURE

16.2. APPENDIX B: AE CLASSIFICATION

16.3. APPENDIX C: INSURANCE CERTIFICATE