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

STUDY TITLE: clinical evaluation of LEft VEntricular Auto threshold algorithm

STATISTISCAL ANALYSIS PLAN ADDENDUM

Version N° 1.2 **Date: 20 April 2018**

	Name	Signature	Date
Prepared by	**Debarshi DEY** Senior Biostatistician	Debarshi DE	20 Apr 2018.
Approved by	**Hanan FAWAZ** Clinical Project Manager		20 Apr 2018.
Approved by	**Giacomo MORDENTI** Director Global Biometrics		20 Apr 2018

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

STUDY TITLE: clinical evaluation of LEft VEntricular Auto threshold algorithm

STATISTISCAL ANALYSIS PLAN ADDENDUM

Version N° 1.2 **Date: 20 April 2018**

	Name	Signature	Date
Prepared by	**Debarshi DEY** Senior Biostatistician		
Approved by	**Hanan FAWAZ** Clinical Project Manager		
Approved by	**Giacomo MORDENTI** Director Global Biometrics		

TABLE OF CONTENT

1. INTRODUCTION

This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the study "IPTL01: LEVEA - clinical evaluation of LEft VEntricular Auto threshold algorithm" in accordance with the Clinical Investigational Plan (CIP) version 1.0 dated 29 Sep 2016, and the e-CRF version 1.0 dated 6 October 2016.

The analysis will be performed by the Department of Global Biometrics at LivaNova in accordance with this SAP.

2. STUDY OBJECTIVES AND STUDY DESIGN

2.1. STUDY OBJECTIVES

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

The secondary objectives are the following:

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

2.1.3. Ancillary objectives

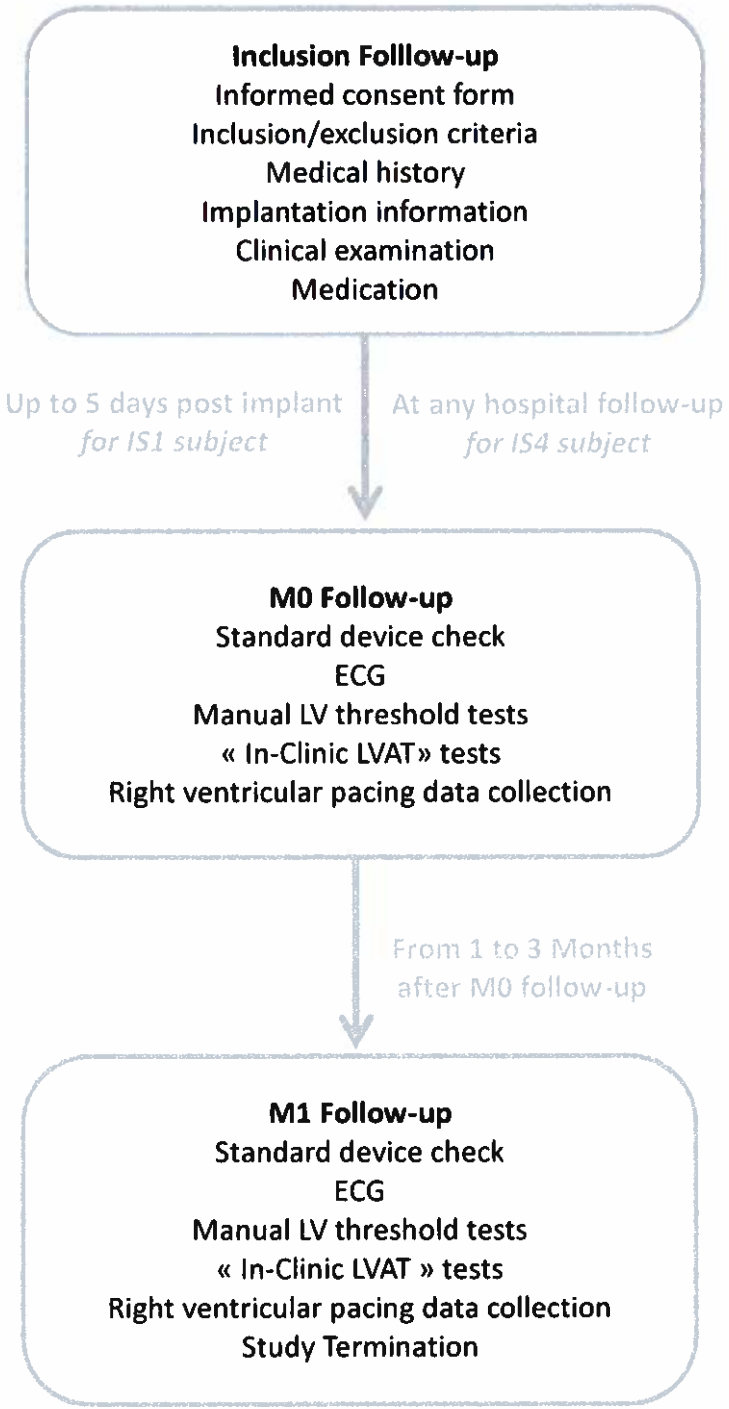
Right ventricular pacing electrograms might be collected and analyzed to identify right ventricular capture and non-capture beats and to assess a right ventricular threshold determination method on Platinium Implantable Cardioverter Device (ICD).

2.2. OVERALL STUDY PLAN

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

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 DF1/IS1 MODEL 1811, DF4/IS1 MODEL 1841 and DF4/IS4 MODEL 1844, interrogated by a clinical programmer able to unlock the function during the clinical evaluation. Thus subjects implanted with these models will be included in the study.



2.3. 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 lower than 90% is rejected.

The following assumptions were made to calculate the sample size:

- Power = 80%
- One-sided alpha = 2.5%
- Null Hypothesis proportion of success-rate (target) = 90%

- Expected success-rate = 95%

With these assumptions, it is required to carry out at least 231 LV vector tests. As we will have 5 different pacing vectors for each subject, we will need 47 (~231/5) subjects.

An attrition rate of 20% is expected for this study.

Thus the number of subjects needed to be enrolled to obtain 47 evaluable subjects = 47/(1-0.2) = 59 subjects.

2.4. RANDOMIZATION

This is a non-randomized study.

3. DOCUMENT AND CHANGE HISTORY

3.1. CHANGES IN ANALYSIS COMPARED TO PROTOCOL

Not applicable.

3.2. SAP AMENDMENT/ADDENDUM RATIONALE AND CHANGE HISTORY

Version	Date	Section(s)	Description of modifications
1.0	19Feb2018		Initial Release.
1.1		13 Mar	Updated Sections: 5.7, 9.1.1, 9.1.2,9.1.3, 10.2, 10.4, 11.1, 12.2, 13.5 It was clarified that for end-points requiring comparison of the algorithm threshold value with the manual threshold value, only those LV tests will be considered for which a non-missing manual threshold value is available. In Section 9.1.1 it is mentioned that only Complete LV tests will be considered to be included in the Analyses, thus number of Attempted will be same as number of completed. Hence, for Decomposition of the success rate of the Primary Endpoint, the number of attempted is redundant and will not be presented. The percentage for Completed LV tests will be calculated based on ITT. Some editorial changes (eg. changing "patient" to "Subject") and additional clarifications (eg. The six and eight LV tests considered for IS1 And IS4 and only IS4 leads respectively) have also been provided.
1.2		10 Apr	Updated Sections: 11.1 B, 11.1 C The reasons for "LV pacing threshold underestimation" and "LV unexpected assessment" will be provided as additional information to understand the underlying causes of under-estimated and

unexpected assessments.

4. OVERVIEW OF PLANNED STATISTICAL ANALYSIS

The study plans only one statistical analysis ("Final statistical analysis").

4.1. INTERIM STATISTICAL ANALYSES

No Interim Analysis is planned for this study.

4.2. FINAL STATISTICAL ANALYSIS

The final statistical analysis will be performed when the last subject has terminated from the study.

The cut-off date for the final analysis will be the date of Last subject Last Visit (Termination visit date of the last subject). The Final analysis will be performed when all the subjects have discontinued from the study, and the database is declared clean and locked.

4.3. OTHER STATISTICAL ANALYSIS

Not applicable

5. DEFINITIONS AND GENERAL METHODOLOGY

5.1. DATE OF INCLUSION

A subject is considered included in the study when the Informed Consent is completed and the subject satisfies all eligibility criteria. Subjects who are screened but do not satisfy the inclusion and exclusion criteria will not be considered enrolled in the study. Inclusion date will be considered as the date on which the subject has satisfied all eligibility criteria and will be obtained from "inclusion page" of the CRF.

5.2. STUDY DAY

The Inclusion date will be considered as the reference start date.

The study day describes the day of the event or assessment date, relative to the reference start date (Inclusion date).

The reference start date is designated as Study Day 1. Study Day –1 is the day that precedes Day 1. Study Day 0 is not defined.

The study day will be calculated as:

- if the event is on or after the reference start date : The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date + 1.
- if the event precedes the reference start date : The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date.

The study day will be displayed in the data listings.

5.3. VISITS , VISIT WINDOWS AND COMPLIANCE

The study has the following scheduled visits:

- Inclusion Visit (up to 5 days post-implant for IS1 subjects and at any time post implant for IS4 subjects)
- M0 follow-up Visit (up to 15 days after inclusion visit)
- M1 follow-up visit (up to 1 to 3 months after M0 visit)

The performed visits have an analysis window defined in the protocol. Study visit days are calculated from the day of inclusion. In addition a Targeted Study Day is defined as the mid-point of the protocol defined Visit window.

Table 1: Visit Windows

Visit	Targeted study day	Analysis window in protocol	Analysis window taken into account in the statistical analysis if scheduled visit is missing
Inclusion	1	0-5 days post-implant for IS1 subjects and at any time post-implant for IS4 subjects	Latest unscheduled visit prior to M0 follow-up visit.
M0	8	0-15 days post-Inclusion Visit	Not Applicable
M1	70	30-92 days post M0 Visit	Not Applicable

All subjects not discontinued from the study on the first day of the window of a respective scheduled visit will be considered as "Eligible".

Subjects having scheduled visits in the protocol defined windows will be considered "compliant". Subjects having scheduled visits outside the protocol visit windows will be considered "non-compliant".

Number and percentage of "eligible" subjects at each visit will be presented, percentage calculated based on the study population.

Number and percentage of subjects who are compliant at each visit will also be presented, percentages will be based on number of "eligible" subjects at the respective visit.

5.4. BASELINE

Assessments performed at the Inclusion Visit will be considered as baseline assessments. If any assessment is missed at the Inclusion visit, then if the assessment is performed at an unscheduled visit prior to the M0 follow-up visit, will be considered as the baseline assessment.

If subjects have no value as defined above, the baseline value will be missing.

5.5. LAST CONTACT DATE

The last contact date is defined as the latest complete date from the list below or the cut-off date, whichever comes first.

- Actual assessment dates (e.g. device electrical performances, Manual LV pacing threshold, ECG record, « In-Clinical LVAT » tests, etc.).
- Adverse events dates
- Device deficiency dates
- Protocol deviation dates
- Date of last recorded on date on "Medications"
- Date of device implant/re-intervention
- Date of Termination

5.6. LV VECTORS AND PACING CONFIGURATIONS

The 14 LV vectors considered in this study are:

Table 2: LV tests

#	IS1 lead	IS4 lead
1	LVtip-LVring	LVtip1-LV2
2	LVtip-RVring	LVtip1-RVring
3	LVtip-RVcoil	LVtip1-RVcoil
4	LVtip-CAN	LVtip1-CAN
5	LVring-RVcoil	LV2-RVcoil
6	LVring-CAN	LV2-CAN
7		LVtip1-LV4
8		LV2-LV4
9		LV3-LV2
10		LV3-LV4
11		LV3-RVring
12		LV3-RVcoil
13		LV3-CAN
14		LV4-RVcoil

Three LV pacing configurations are considered in this study to perform "In-Clinic LVAT" tests for all eligible LV pacing vectors:

- DDD A-test (atrium overdrive)
- DDD P-test (no atrium overdrive)
- VVI test

5.7. LV VECTOR TEST

"In-Clinic LVAT" test is composed of several LV Vector Tests, each corresponding to a selected LV pacing vector (out of a possible 14 LV vectors).

The following definitions apply when performed on the same subject, with the same pulse width (In order to be comparable, the pacing width between automatic tests (any of them) and manual test needs to be strictly similar), on the same LV pacing vector and at the same visit:

- Attempted LV Vector test: If a LV Vector test, corresponding to an available LV pacing vector, was not launched during a visit then the LV Vector test will be classified as "Not Attempted", and otherwise "Attempted". That is, if an LV Vector test which was launched and neither interrupted nor aborted, it will be considered as "Attempted".
- A complete LV Vector Test: test was performed (not aborted or interrupted) and a threshold value is provided by the algorithm. A LV Vector test resulting to a "no capture or high pacing threshold > 5V" at starting amplitude is considered as a complete LV Vector test. If a test was not aborted/neither interrupted and has no value, then the test will be considered as attempted but not completed.

  The conditions for Attempted, Aborted and Interrupted can be further understood from the following table:

Table 3: Conditions for Completed LV test

Attempted	Aborted = Yes or No	Interrupted = Yes or No	Complete	Threshold Value
No	NA*			
Yes	Yes	No	No	Missing
Yes	No	Yes	No	Missing
Yes	No	No	Yes	Not missing

* Corresponding data is missing.

- A successful LV Vector Test: threshold value provided automatically by the algorithm is equivalent to the manual threshold test done by the physician among the complete LV Vector Tests.

An LV threshold value obtained from the device algorithm (automatic) will be considered as equivalent to the manual threshold value if the automatic and manual LV threshold tests has the same value, with the same pacing pulse width, with a flexibility of ± 2 steps (meaning ±0.5V if threshold<2.5V, else ±1V. A margin of ± 2 steps is accepted because of the variability of the threshold, and due to the design of the algorithm.

The equivalent range for the Algorithm for a Manual threshold is provided in the table below:

Table 4: Equivalent ranges for Successful LV tests (Manual vs. Algorithm)

Manual Threshold value obtained (in V)	Equivalent Range of the Algorithm (Automatic threshold) (in V)
7	>5
6	>5
5	>4.0
4.5	3.5-5.0
4.0	3.0-5.0
3.5	2.5 - 4.5
3.0	2.25 - 4.0
2.75	2.25 -3.5
2.5	2- 3.5
2.25	1.75-3
2.0	1.5-2.5
1.75	1.25-2.25
1.5	1.0-2.0
1.25	0.75-1.75
1	0.5-1.5
0.75	0.25-1.25
0.5	0.25-1.0

0.25	0.25-0.75

Note: if an LV test is reported to be done, but no manual threshold value is present, it will be imputed as "Missing".

- 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.

As values determined by the algorithm are not displayed on the programmer screen, data are stored in the electronic Real-Time Data (RTD) files that are loaded in the electronic Case Report Form (eCRF) in order to be extracted by the sponsor.

- Diagnostic accuracy is defined as an accurate adjudication by an independent reviewer 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 LV threshold value provided by the algorithm compared to the reviewer adjudication is considered accurate if the difference is within ± 1 step.

  The "Accurate" range for the Independent Reviewer for a Algorithm (Automatic) threshold is provided in the table below:

Table 5: Equivalent ranges for Accurate LV tests
(Algorithm vs. Independent reviewer)

Threshold value obtained with the algorithm (Automatic) (in V)	Accurate Range (Independent reviewer)
>5	>5
5.0	>4.5
4.5	4.0-5.0
4.0	3.5-4.5
3.5	3.0-4.0
3.0	2.5-3.5
2.5	2.25- 3
2.25	2.0-2.5
2.0	1.75-2.25
1.75	1.5-2.0

1.5	1.25-1.75
1.25	1.0-1.5
1.0	0.75-1.25
0.75	0.5-1.0
0.5	0.25-0.75
0.25	0.25-0.5

- Assessment of LV pacing threshold underestimation: comparison to manual LV threshold value will be performed by comparing manual and automatic LV threshold values at each visit. 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 (meaning -0.5V if threshold<2.5V, else -1V as measured) .

Table 6: Ranges for Under-estimated LV tests (Manual vs. Algorithm)

Manual Threshold value obtained (in V)	Under-estimated if - Automatic threshold value (in V)
7	< 5
6	<4.5
5	< 4.0
4.5	<3.5
4.0	<3.0
3.5	<2.5
3.0	<2.25
2.75	<2.25
2.5	<2.0
2.25	<1.75
2.0	<1.5
1.75	<1.25

Manual Threshold value obtained (in V)	Under-estimated if - Automatic threshold value (in V)
1.5	<1.0
1.25	<0.75
1	<0.5
0.75	Not Applicable
0.5	Not Applicable
0.25	Not Applicable

Note: if an LV test is reported to be done, but no manual threshold value is present, it will be imputed as "Missing".

5.8. Subgroup Definitions

Not applicable

6. Analysis Population

6.1. Included Population (IP)

The included population consists of all subjects included in the study who have completed "Inclusion Form".

6.2. Evaluable Population (EP)

The evaluable population will consist of IP excluding the subjects having a protocol deviation on "Eligibility Criteria: Right atrial, right and left ventricles lead must be implanted. Only Bipolar or quadripolar for left ventricular lead". A subject whose termination date occurred prior to M0 visit, will be excluded from this population.

6.3. Intention to Treat Population (ITT)

The Intention To Treat (ITT) population consists of all subjects from EP with at least 1 eligible complete LV Vector Tests at M0 or M1 visit.

6.4. M0- Intention to Treat Population (M0-ITT)

The M0-Intention To Treat (M0-ITT) population consists of all subjects from ITT with at least 1 eligible complete LV Vector Tests at M0 visit.

6.5. M1- Intention to Treat Population (M1-ITT)

The M1-Intention To Treat (M1-ITT) population consists of all subjects from ITT with at least 1 eligible complete LV Vector Tests at M1 visit.

6.6. Ancillary Population (AP)

The Ancillary Population (AP) consists of all subjects in IP with at least one right ventricular pacing electrogram collected at the M0 or M1 visit.

6.7. Per-Protocol Populaton (PP)

The per-protocol population consists of all subjects in the EP who do not have any major protocol deviation (as classified in the eCRF) that could impact the interpretation of the primary analyses conducted on ITT.

The major protocol deviations will be identified as follows:

- Manual: These major protocol deviations will be identified at the time of the final data review meeting by means of listings provided by Global Biometrics. The identification of the major protocol deviations will be conducted by Data review team.

7. Disposition

7.1. Subject Disposition

The number and percentage of subjects in each analysis population defined in Section 7 will be presented. The percentage will be calculated based on IP.

Disposition of subjects will be presented on IP.

The following summaries will be provided (% based on the total number of IP subjects):

- Number (%) of subjects who are included in the study
- Number (%) of subjects who had completed Inclusion, M0 and M1 visits.
- Number (%) along with reasons, of subjects who discontinued the study (based on Termination page) between Inclusion and M0 visits, between M0 and M1 visits, and after M1 visit.
- Number (%) of subjects who are in IP, EP, ITT, M0-ITT, M1-ITT, AP, PP

7.2. Protocol Deviations

Major protocol deviations will be analyzed based on IP, ITT and M0-ITT, M1-ITT and information will be taken from "Protocol Deviation" page in eCRF.

- The number (%) of subjects by deviation category (description)

The protocol deviations leading to exclusion from analysis sets will be tabulated separately.

All (major and minor) protocol deviations will be listed.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1. SUBJECT DEMOGRAPHICS

Subject demographics will be presented on the IP.

This analysis will include the following:

- Age (Years)
- Gender (Male/Female)
- Height (in m)
- Weight (in kg)
- Body Mass Index (BMI-kg/m^2)
- NYHA

8.2. IMPLANT CHARACTERISTICS

The following implant characteristics will be analyzed by means of summary statistics in the IP analysis population.

i. Pulse generator Manufacturer - Number and percentage of subjects with either of the three
    - o Platinium CRT-D SONR, 1811
    - o Platinium CRT-D SONR, 1841
    - o Platinium CRT-D SONR, 1844

ii. RA Lead Manufacturer – Number and percentage of subjects with one of the following RA lead manufacturer:
    - o SORIN
    - o Medtronic
    - o St Jude Medical
    - o Boston Scientific
    - o Biotronik
    - o Other

iii. RV Lead Manufacturer – Number and percentage of subjects with one of the following RV lead manufacturer:

- o SORIN
- o Medtronic
- o St Jude Medical
- o Boston Scientific
- o Biotronik
- o Other

iv. LV Lead Manufacturer – Number and percentage of subjects with one of the following LV lead manufacturer:

- o SORIN
- o Medtronic
- o St Jude Medical
- o Boston Scientific
- o Biotronik
- o Other

Summary statistics for the following variables will be provided on EP for all visits

i. Summary statistics for RA and RV Pacing Threshold
ii. Summary statistics for RA and RV Pacing Width
iii. Summary statistics for LV Pacing Threshold
iv. Summary statistics for LV Pacing Width
v. Summary statistics for RA, RV, LV impedances
vi. Summary statistics for RA, RV sensing amplitudes

8.3. MEDICAL HISTORY

Medical history will be summarized in IP. Descriptive statistics (mean, median, standard deviation, 95% CI of mean, Q1, Q3, minimum and maximum) will be presented for continuous variables. The number and percentage of subjects in each category will be presented for categorical variables. The number and percentage of subjects with missing data will be provided.

8.4. PRIOR AND CONCOMITANT MEDICATION

Medications at enrollment and at termination visit obtained from the Medication eCRF page will be presented for IP. Only Cardiovascular medications are recorded.

Prior and Concomitant Medications will be summarized and sorted alphabetically. The number (and percentage) of subjects will be displayed for each kind of medication.

Medications will be summarized showing number and percentage of subjects with at least one medication at enrollment and at each visit (Inclusion, AE visits, Termination visit).

Medications will be considered as per coding by Safety officer.

9. PRIMARY EFFICACY ANALYSES

9.1. PRIMARY ENDPOINT ANALYSIS

9.1.1. PRIMARY ENDPOINT

The primary endpoint of the study is the success rate of "In-Clinic LVAT" test, that is the (Number of successes/Total Number of completed LV vector tests excluding the tests for which Manual tests are missing) of the "In-Clinic LVAT" feature.

For the primary endpoint, the evaluation is performed on 5 LV pacing vectors common to IS1 and IS4 leads:

Table 7: LV tests for Primary Endpoint

#	IS1 lead	IS4 lead
1	LVtip-LVring	LVtip1-LV2
2	LVtip-RVcoil	LVtip1-RVcoil
3	LVtip-CAN	LVtip1-CAN
4	LVring-RVcoil	LV2-RVcoil
5	LVring-CAN	LV2-CAN

Test will be evaluated at different LV pacing conditions: DDD A-test and VVI test. 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 (same pacing pulse width) and reported in the electronic Case Report Form (eCRF) will be retained. In case several LV Vector Tests were eligible with the same LV pacing vector, for the same subject, on 2 different visits, only M0 data will be considered.

The primary analysis is based on manual tests which are non-missing and for which complete LV Vector Tests are provided by the algorithm and collected at M0. If data at M0 is unavailable, then corresponding data collected at M1 will be considered.

To summarise, the following table mentions the adequate LV pacing configuration to be considered for the LV Vector test for the Primary Analysis:

Table 8: LV tests for Primary Analysis

Cases	Visit	LV pacing Configuration		Which one to use?
		DDDA-test	VVI test	

Cases	Visit	LV pacing Configuration		Which one to use?
		DDDA-test	VVI test	
Case 1	M0	Available	Available	Use DDD A-test
Case 2	M0	Available	Unavailable	Use DDD A-test
Case 3	M0	Unavailable	Available	Use VVI test
Case 4	M0	Unavailable	Unavailable	Go to M1
	M1	Will be considered only for Case 4		
Case 5	M1	Available	Available	Use DDD A-test
Case 6	M1	Available	Unavailable	Use DDD A-test
Case 7	M1	Unavailable	Available	Use VVI test
Case 8	M1	Unavailable	Unavailable	Unavailable

9.1.2. STATISTICAL TEST OF PRIMARY ENDPOINT

The Null hypothesis: Success rate of the "In-Clinic LVAT" feature < 90%.

The alternative hypothesis: Success rate of the "In-Clinic LVAT" feature ≥ 90%.

Each LV vector test will be categorized as a success if the automatic and manual LV threshold test has an equivalent LV threshold value, and failure otherwise. The definition of an equivalent LV threshold value is provided above in Table 4.

The success rate of "In-Clinic LVAT" test is defined as: Number of successes/Total Number of completed LV vector tests (excluding the tests for which Manual test is missing).

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 success rate and 95% exact CI (Clopper & Pearson, 1934) will be presented.

DECOMPOSITION OF PRIMARY ENDPOINT SUCCESS RATE BY LV VECTOR AND BY CONFIGURATION

Total number of completed and successful LV vector tests considered for the Primary Analysis will be presented by:

i. LV vector tests considered with DDD A-test LV pacing configuration at M0 visit. The break up of the five LV vectors will also be presented.

ii. LV vector tests considered with VVI test LV pacing configuration at M0 visit. The break up of the five LV vectors will also be presented.

iii. LV vector tests considered with DDD A-test LV pacing configuration at M1 visit. The break up of the five LV vectors will also be presented.

iv. LV vector tests considered with VVI test LV pacing configuration at M1 visit. The break up of the five LV vectors will also be presented.

Only those LV tests will be considered for which manual tests are non-missing. For number of LV vector tests "completed", the percentage will be calculated based on ITT.

For number of LV vector tests "Successful", the percentage calculated based on number of LV vector tests "completed".

All LV vector test results will be listed.

9.1.3. SUPPORTIVE AND SENSITIVITY ANALYSIS FOR PRIMARY ENDPOINT

i. 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 (excluding the tests for which Manual test is missing) 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. The prior and the posterior density function will also be plotted.

ii. In case the number of completed LV Vector Tests (M0 and M1 combined) is less than 231 and the primary endpoint null hypothesis is rejected, Tipping Point Analysis will be performed. Primary analysis will be repeated by shifting the status of subjects with missing primary endpoint value in order to assess the combination of results which will move the performance results from significant to non-significant. A 95% CI will be presented for each shift parameter.

iii. The Primary analysis will be repeated excluding the subjects with major protocol deviations from the subjects considered for the primary analysis.

10. SECONDARY EFFICACY ANALYSES

Secondary and Ancillary endpoints will be assessed at all visits using descriptive statistics. Point estimates and exact CI (Clopper & Pearson, 1934) will be presented wherever possible.

Whenever a Statistical test is performed for a Secondary Endpoint, it is of hypothesis generating and descriptive in nature.

10.1. ASSESSMENT OF DIAGNOSTIC ACCURACY OF "IN-CLINIC LVAT" TEST AT M0 VISIT: INDEPENDENT REVIEWER VALIDATION OF LV THRESHOLD VALUE PROVIDED BY ALGORITHM

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

Diagnostic accuracy is defined as an accurate adjudication by an independent reviewer 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 LV threshold value provided by the algorithm compared to the reviewer adjudication is considered accurate if the difference is within ± 1 step (meaning ±0.25V if threshold<2.5V, else ±0.5V as measured). The definition of an Accurate LV threshold value is provided above in Table 5.

In case the algorithm and the reviewer adjudication provide both a LV threshold value equal to ">5V" (the LV vector test has resulted in "no capture" or "threshold value higher than 5V at starting amplitude), the LV threshold value is considered accurate. Number and percentages of "accurate" and "inaccurate" matches will be presented along with the exact 95% CI (Clopper & Pearson, 1934).

This analysis will be performed on M0-ITT population.

Decomposition of Diagnostic Accuracy by LV Vector and by LV pacing configuration

Total number of attempted, completed, and accurate LV vector tests will be presented by LV vector for each LV pacing configuration.

For the LV tests performed for subjects with either IS1 and IS4 leads (six LV vectors common to IS1 and IS4), the percentage for the number of LV vector tests "attempted", will be calculated based on the number subjects implanted with either IS1 and IS4 leads.

For the LV tests performed for patients with IS4 leads(eight LV vectors pertaining only to IS4), the percentage for the number of LV vector tests "attempted", will be calculated based on the number of patients implanted with IS4 lead.

For number of LV vector tests "completed", the percentage will be calculated based on the number of LV vector tests attempted and for number of LV vector tests "accurate", the percentage calculated based on number of Complete LV vector tests .

A heat plot will be presented for Attempted, Completed and Accurate percentages. If the percentage is > 90%, it will be coloured green, if the percentage is between 75% and 90% (inclusive), it will be coloured brown and if the percentage <75%, then it will be coloured orange.

This will also be listed.

For this analysis, EP will be used considering M0 visit only.

10.2. ASSESSMENT OF THE SUCCESS RATE OF "IN-CLINIC LVAT" TEST AT M0 VISIT: COMPARISON TO MANUAL LV THRESHOLD TESTS RESULTS

This endpoint is the success rate of "In-Clinic LVAT" feature on LV pacing vectors and LV pacing configurations available at M0 visit.

The threshold obtained from the "In-Clinic LVAT" feature, extracted from RTD files, will be compared against manual LV threshold values recorded in the eCRF. The definition of equivalence is same as that of primary analysis.

Test will be evaluated at different LV pacing configuration: DDD A-test, DDD P-test and VVI test. Among all the eligible complete LV Vector Tests collected, only those with a manual LV threshold test performed in the same conditions (same pacing pulse width) at M0 visit and reported in the electronic Case Report Form (eCRF) will be retained.

All analyses performed for this Secondary endpoint will be performed based on manual LV threshold tests results considering data only from M0 visit (except for testing of hypothesis and missing data imputation).

This Secondary endpoint will be based on M0-ITT population.

Decomposition of "In-Clinic LVAT" Success Rate by LV Vector and by LV pacing configuration at M0 visit

Only subjects with non-missing manual data will be considered.

Total number of attempted, completed and successful LV vector tests will be presented by LV vector for each LV pacing configuration.

For number of LV vector tests "attempted", the percentage will be calculated based on the EP population.

For number of LV tests "completed", the percentage will be calculated based on the number of LV vector tests attempted.

For number of LV vector tests "Sucessful", the percentage will be calculated based on number ofComplete LV vector tests.

A heat plot will be presented for Attempted, Complete and Success percentages. If the percentage is > 90%, it will be coloured green, if the percentage is between 75% and 90% (inclusive), it will be coloured brown and if the percentage <75%, then it will be coloured orange.

For this analysis, EP will be used considering M0 visit only.

10.3. ASSESSMENT OF THE SUCCESS RATE OF "IN-CLINIC LVAT" TEST AT M1 VISIT: COMPARISON TO MANUAL LV THRESHOLD TESTS RESULTS

This endpoint is the success rate of "In-Clinic LVAT" feature on LV pacing vectors and LV pacing configurations available at M1 visit.

The analysis performed for this objective will be exactly similar to that performed for Secondary Objective # 2, but for M1-visit.

For this analysis, M1-ITT population will be used.

For the Decomposition analysis, EP will be used considering M1 visit only.

10.4. 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 (VV delay). A subject is defined as "eligible" if he/she has at least one complete LV vector test in either of the M0 or M1 visit.

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

A. The number and percentage of subjects who are "eligible" to receive the algorithm. Percentage will be calculated based on the total number of subjects included in the EP, that is:

   Number of subjects with at least one complete LV Vector Test at M0 or M1 visits/ Total Number of subjects in EP.

B. For subject having IS1 lead, up to 6 LV vector tests over 3 LV pacing configurations will be attempted for each subject at each visit.

   Among all the subjects having IS1 leads, the number and percentage of subjects having no, one, two,.., six Attempted, Completed and Successful LV vector tests will be presented by LV pacing configuration and visit.

   Among all the subjects having IS4 leads, the number and percentage of subjects having one, two,.., fourteen Attempted, Completed and Successful LV vector tests will be presented by LV pacing configuration and visit.

   Only subjects with non-missing manual data will be considered.

   Percentages calculated based on the number of subjects in EP with the respective lead and configuration will be presented for Attempted, Completed and Successful LV tests.

   This information will also be presented with the help of histograms.

   This analysis will be based on EP.

   This will also be listed.

11. SECONDARY SAFETY ANALYSES

11.1. ASSESSMENT OF THE DEVICE CHARACTERESTICS IN TERMS OF SAFETY AND DEVICE DEFICIENCY

A. Serious adverse device events and device deficiencies will be collected during each subject visit. Confirmation of absence of USADE during "In-Clinic LVAT" tests will be evaluated by analyzing all SAEs and device deficiencies (DD) collected at each visit.

   This secondary endpoint will be based on IP.

B. Algorihthm caracteristic: Underestimated Assessments

   Assessment of LV pacing threshold underestimation: comparison to manual LV threshold value will be performed by comparing manual and automatic LV threshold values at each visit. 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 (meaning -0.5V if threshold<2.5V, else -1V as measured) . Please see table 6.

Number and percentages of "underestimated" assessments will be presented along with the exact 95% CI (Clopper & Pearson, 1934) by M0 and M1 visit. Only subjects with non-missing manual data will be considered.

The reasons for LV pacing threshold underestimation at M0 visit will be presented as table and listing. The missing reasons (if any) for underestimation will be presented as "Not available". For the table, the number and percentages of the reasons will be presented with the denominator of the percentages based on the total number of LV pacing threshold underestimated.

Total number of attempted, completed,, Underestimated LV vector tests will be presented by LV vector for each LV pacing configuration by visit.

For the LV tests performed for patients with either IS1 and IS4 leads (six LV vectors common to IS1 and IS4) , the percentage for the number of LV vector tests "attempted", will be calculated based on the number of patients implanted with either IS1 and IS4 leads.

For the LV tests performed for patients with IS4 leads (eight LV vectors pertaining only to IS4), the percentage for the number of LV vector tests "attempted", will be calculated based on the number of patients implanted with IS4 lead.

For number of LV vector tests "completed", the percentage will be calculated based on the number of LV vector tests attempted.

For number of LV vector tests "Underestimated", the percentage calculated based on number of Complete LV vector tests .

A heat plot will be presented for Attempted, Complete, Underestimated percentages. If the percentage is > 90%, it will be coloured green, if the percentage is between 75% and 90% (inclusive), it will be coloured brown and if the percentage <75%, then it will be coloured orange.

This Secondary endpoint will be based on EP population and will also be listed.

C. Analysis of Unexpected Function Operations

Number and percentage of unexpected function operations by analyzing EGM collected in the RTD files and ECG (from DDD A-test) performed during "In-Clinic LVAT" test at each visit will be presented.

i. Number and percentage of LV vector tests with unexpected functions based on all LV vector tests attempted.

ii. Number and percentage of LV vector tests with unexpected functions per LV vector per LV pacing configuration per visit

Total number of attempted, completed, with expected function, with unexpected function LV vector tests will be presented by LV vector for each LV pacing configuration by visit.

For the LV tests performed for subjects with either IS1 and IS4 leads six LV vectors common to IS1 and IS4), the percentage for the number of LV vector tests

"attempted", will be calculated based on the number of subjects implanted with either IS1 and IS4 leads.

For the LV tests performed for patients with IS4 leads (eight LV vectors pertaining only to IS4), the percentage for the number of LV vector tests "attempted", will be calculated based on the number of patients implanted with IS4 lead.

For number of LV vector tests "completed", "with Unexpected Function" and "with Expected Function", the percentage will be calculated based on the number of LV vector tests attempted .

The reasons for unexpected assessement at M0 visit, M1 visit and overall will be presented as table and listing. The missing reasons (if any) for unexpected assessement will be presented as "Not available". For the table, the number and percentages of the reasons will be presented with the denominator of the percentages based on the total number of unexpected assessements.

All unexpected function operations will be listed.

This Secondary endpoint will be based on EP population.

12. ANCILLARY ENDPOINT ANALYSES

Whenever a Statistical test is performed for a Ancillary Endpoint, it is of hypothesis generating and descriptive in nature.

12.1. CAPTURE CYCLES AND NON-CAPTURE CYCLES OF RIGHT VENTRICULAR PACING ELECTROGRAMS

Right ventricular pacing electrograms will 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).

The analysis is based on RV electrogram strips. Each subject will have 4 electrograms recorded: at 5V, 2V; 1.5V and 1V RV pacing test. Each electrogram is a 20 sec EGM recording, that is, 20 sec of cardiac beat. Each RV electrogram is composed of cardiac beat cycles; each of them can results in capture or non-capture of the right ventricle depolarization .

The number and percentage of accurate captures (accurate discrimination between capture/non-capture cycles) based on all cycles will be presented by RV pacing configuration (RV-P test and RV-A test) and by visit. A 95% CI will be presented.

Barplots for the same will be provided.

This will also be listed by subject.

This analysis will be based on AP.

12.2. SUCCESS-RATE BASED ON SUBJECTS

A subject will be considered "success" if there is at least one LV vector test successful among all LV vector tests performed for all LV pacing configurations in either of the two subject visits.

The number and percentage of "successful" and "unsuccessful" subjects will be presented. 95% exact CI will be provided.

Only subjects with non-missing manual data will be considered.

This analysis will be based on ITT.

13. ADDITIONAL EXPLORATORY ANALYSIS

Whenever a Statistical test is performed for an Additional Analysis, it is of hypothesis generating and descriptive in nature.

13.1. ACCURATE DETERMINATION OF HIGH PACING THRESHOLD VALUE (NO CAPTURE OR >5V) : ALGORITHM VS. INDEPENDENT REVIEWER

All LV vector tests are done at a starting amplitude of 5V for all LV pacing configurations. Therefore, if the LV threshold value is > 5 V or if there is no capture at the starting amplitude for the tested LV vector, then the algorithm identifies the LV threshold value as a high pacing threshold "> 5V".

Number and percentage of correct determination of high pacing threshold value (>5V) provided by the algorithm feature and an independent reviewer, on all LV pacing vectors and all LV pacing configurations available at M0 visit will be presented. Percentage will be based on all subjects included in the M0-ITT.

A Fisher exact test will be performed to test the significance of association between accurate determination provided by the algorithm feature and the independent reviewer. The two-sided p-value will be presented.

In addition, the Sensitivity and Specificity as defined below will also be presented:

i. Sensitivity or Probability (Algorithm feature = High Pacing Threshold | Independent reviewer = High Pacing Threshold) = TP/(TP+FN)

i. Specificity or Probability (Algorithm feature = Not High Pacing Threshold | Independent reviewer = Not High Pacing Threshold) = TN/(FP + TN)

13.2. ASSESSMENT OF CONSISTENCY OF "IN-CLINIC LVAT" TEST BETWEEN M0 AND M1 VISITS: COMPARISON TO MANUAL LV THRESHOLD TESTS RESULTS

At each of the two subject visits, success rate will be calculated for each LV vector and each LV pacing configuration based on M0-ITT and M1-ITT respectively. As we have up to 14 LV vectors and 3 configurations, we will have a total of 42 success rates at each M0 and M1 visits.

Null Hypothesis: The Success-rate for LV tests at M0 visit = The success rate for LV tests at M1 visit

Alternative Hypothesis: The Success-rate for LV tests at M0 visit ≠ The success-rate for LV tests at M1 visit.

A paired t-test will be performed to test if the mean difference of the success rate over the two visits is significantly different from 0. A two-sided p-value will be presented.This will be performed by configuration and overall. The mean difference and its 95% CI will also be presented.

This analysis will be performed on ITT.

13.3. EVALUATION OF APPLICABILITY OF THE ALGORITHM: DISTRIBUTION OF INTRINSIC CHARACTERISTICS

The distribution of PR/VV delay/AR will be presented by "Eligible" and "not eligible" subjects. An "eligible" subject is one who has at least one complete LV vector test.

The Categories for PR parameters to be considered are :

i. PR < 120 ms

ii. 120 ⩽ PR ⩽ 200

iii. PR > 200 ms

The Categories for VV delay parameters to be considered are:

i. VV ⩽ 234 ms

ii. VV > 234 ms

The Categories for AR parameters are

i. AR < 170 ms

ii. 170 ⩽ AR ⩽ 250 ms

iii. AR > 250 ms

Chi-square tests will be performed to test if there is an association between eligibility of a subject to the algorithm and the distribution of PR/VVdelay/AR. Two sided p-values will be presented along with a table to present the frequency count of applicability(eligibility) of algorithm (Yes/No) and the distribution of PR/VV delay/AR.

This will be analysed by visit. The analysis will be based on EP.

The population used is EP population

13.4. DISTRIBUTION OF QRS BY VISIT

The QRS values collected for each subject will be presented as summary statistics by visit and overall. They will also be presented by means of a Box Plot.

The number and percentage of subjects with the following categories for QRS parameters will be presented:

i. QRS ⩽ 100 ms

ii. 100 < QRS ⩽ 120 ms

iii. QRS > 120 ms

This analysis will be based on EP.

13.5. DISTRIBUTION OF THE LV PACING THRESHOLD MEASURED PER LV PACING VECTOR IN "IN-CLINIC LVAT" ALGORITHM

The possible LV pacing thresholds measured by each LV pacing vector at each LV pacing configuration are: 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.5, 4.00, 4.50, 5.00 .

A frequency distribution of the categories ≤2.5V, 2.5V - ≤3.5V, 3.5V – ≤5V, >5V, and a Histogram will be plotted by configuration and visit.

For the LV tests performed for subjects with either IS1 and IS4 leads six LV vectors common to IS1 and IS4), the percentage will be calculated based on the number of subjects implanted with either IS1 and IS4 leads.

For the LV tests performed for subjects with IS4 leads (eight LV vectors pertaining only to IS4), the percentage will be calculated based on the number of subjects implanted with IS4 lead.

This analysis will be based on ITT.

13.6. DISTRIBUTION OF THE LV IMPEDANCE PER VISIT

The possible LV impedance measured is between 200 and 3000 Ohms at M0 and M1 visit.

Summary Statistics of LV impedance measured will be presented by visit and overall. A Box-plot of the same will also be plotted.

This analysis will be based on EP.

14. SAFETY ANALYSIS

Adverse events definitions are derived from ISO 14155:2011 - Clinical investigation of medical devices for human subjects.

14.1. GENERAL RULES FOR AE REPORTING

Adverse events that occurred after the inclusion visit and prior to study termination or Lost-to follow-up will be presented for all subjects in the Safety Population.

If there are less than 10 Adverse events reported in the study, the Adverse Events will be reported only by listing.

The following Safety Events will be reported in the study based on their time of occurrence:

<u>During initial testing procedure</u>

- All adverse events e.g. procedural complications (serious and non-serious), excluding direct and clinically expected physiologic effects of testing

<u>Throughout the study</u>

- All Serious cardiovascular and access site Adverse Events
- All deaths

- Unanticipated (Serious) Adverse Device Effect
- Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) with or without associated adverse events

The classification of AEs for statistical analysis will be based on site-reported events for the final diagnosis in the Safety populations.

A positive relationship (YES) will include those assessed as related or unknown if related to the device/procedure. A negative relationship (NO) will be limited to those assessed as not being related to the device/procedure.

The adverse events (AEs) in the Safety population will be assessed using descriptive statistics by

- Diagnosis (AE Category, AE Term, AE clarifiers)
- Relationship – (Yes/No)
- Device Interrogation (Yes/No)
- Treatment and Medication
- Outcome (Resolved/Death/Pending)
- Relationship: to procedure, to device
- Expectedness for ADE (Yes/No)

14.2. ANALYSIS OF ADVERSE EVENTS

The following AE summaries will be produced for all subjects in Safety set:

Overall Summary of AEs, ADEs, Device Deficiencies, SAEs and Deaths will be provided for number of subjectsubjects with at least one event and number of events

- Any AEs
  - Expected
  - Unexpected
  - Was Device Interrogation performed (Yes/No)
  - Related to procedure (Yes/No)
  - Related to device (Yes/No)
  - Outcome (Resolved/Death/Pending)
- Any ADEs
  - Expected
  - Unexpected
  - Was Device Interrogation performed (Yes/No)
- Any Device Deficiencies
  - Expected
  - Unexpected

- Issue resulted in any (serious) adverse event(Yes/No)
- Was reprogramming done (Yes/No)
- Device re-intervention (Yes/No)
- Device returned to Sorin (Yes/No)
- Subject discontinued from the study following the DD(Yes/No)

- Serious adverse events (SAEs)
- SAE (Other than Death)
- SAE Leading to Death
- Deaths
- Device related
  - ✓ Unexpected Serious Adverse Device Effect (SADE)
  - ✓ Expected SADE
- Procedure related
- Not device or procedure relationship
- Device related ISO (procedure and/or device related)
  - Unexpected Serious Adverse Device Effect (SADE)
  - Expected SADE

For the following -

- AEs
- ADEs
- Device deficiencies
- SAEs

events leading to Hospitalization will be analysed with the following details:

- Hospitalization required (Yes/No)
- Duration of Hospitalization (Summary statistics – Mean, SD, Q1, Median, Q3, Min, Max)
- Did it cause Permanent Disability/incapacity (Yes/no)
- Intervention to Prevent Life Threatening Injury or Permanent Damage (yes/No)
- Life Threatening Illness or Injury (Yes/No)

For the following -

- AEs
- ADEs

- Device deficiencies
- SAEs

  events requiring treatment or medication will be analysed to provide the following:

  - Treatment provided (Yes/No)
  - Device programming required (Yes/No)
  - Device re-intervention required (Yes/No)
  - Any other intervention required (Yes/No)
  - Led to change in cardiovascular medication since last visit (Yes/No)

For the following -

- AEs
- ADEs
- Device deficiencies
- SAEs

  Outcome will be reported. Outcome can be any of the following:

  - Final outcome pending
  - Final outcome
    - Resolved
    - Death
    - On-going or chronic
    - Unknown

The following information for Device deficiencies will be summarized:

- Component involved (obtained from Device deficiency page of eCRF)
- Device Deficiency category (obtained from Device deficiency page of eCRF)
- Resulted in AE (obtained from Device deficiency page of eCRF)
- Resulted in SAE

All AEs,ADEs, Device Deficiencies,SAEs and Deaths will be listed.

15. 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
DD	Device Deficiency
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
IRB	Institutional Review Board
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
RTD / DTR	Real-Time Data
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

16. REFERENCES

17. APPENDICES 1: ANALYSIS SPECIFICATION

17.1. GENERAL PRINCIPLES

The statistical analysis will be performed on the analysis study database with appropriate software, SAS® Software version 9.4 or above (SAS Institute, Cary, N.C.).

Where a listing or table has been planned, but no data meet the criteria, then a single line stating 'No data meeting the criteria are present' will be provided in the output.

All the data collected and derived in the trial will be presented in subject data listings.

17.2. DESCRIPTIVE STATISTICS

Descriptive statistics will be calculated using as reference the number of subjects in the relevant analysis population (any exception will be specified) according to the nature of the data as follows:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation, 95% CI, minimum and maximum values, median and quartiles (Q1, Q3).

  If there are fewer than 5 observations only the number of non-missing observations, arithmetic mean, median, minimum and maximum will be presented.

- Categorical variables: Number of non-missing observations, the number of missing and the relevant percentage on the analysis population, number and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects with non-missing information.

In case of subcategories, the relative frequencies will be calculated on the basis of the subjects in the respective category, in this case a footnote will be added explaining the different denominators.
For presentation of missing data, please see section 6.10.

17.3. PERCENTAGES AND DECIMAL PLACES

For continuous variables, minimum and maximum will be presented to the same precision as the raw data. Mean, median, Q1 and Q3 will be presented to one more decimal place and standard deviation to two more decimal places than the raw data.

For categorical variables, percentages will be presented up to two decimal places.

17.4. PRESENTATION OF DATES

Calendar dates and times (optional) in all the listings will be displayed in the format:

YYYY-MM-DD Thh:mm:ss e.g. 2011-01-15 T10:20 :23.

Note: If time is not collected, calendar dates will be displayed as: YYYY-MM-DD.

17.5. TIME UNITS

The standard unit of time for this study will be days, unless otherwise specified.

In case duration is to be reported in months, duration in days is divided by 30.4375.

If duration is to be reported in years, duration in days will be divided by 365.25.

17.6. GENERAL CONVENTIONS FOR MISSING DATA

For the statistical analysis, some particular data handling conventions (handling of missing data, pooling of centers) are planned. The details are present in the respective Sections. While presenting summary statistics and in Listings the following conventions will be used with respect to missing data:

Missing data	Will be reported as "Not Available"

Data reported as, "Not done", "Asked but unknown" ," Not asked"	Will be reported as " Unknown"
Data reported as "Not applicable", "Measurement failed"	Will be reported as "Not applicable"
Reported data is not valid	Will be reported as invalid data
Adverse events Missing or partially missing start date	Missing day NK-MMM-YYYY To be imputed by: 1st day of the month Missing day and month NK-NK-YYYY To be imputed by: 1st Day of the year. Totally missing date NK-NK-NK To be imputed by: Reference Start date. Should not happen, should have been clarified at the data level. In case of not resolved.

17.7. DATA INCLUDED IN THE ANALYSES AND CUT-OFF DATE

The final analyses will be performed using all data collected in the database up to the data cut-off date. Of all the termination dates of the subjects included in the study , the last termination visit date will be defined as the cut-off date and will be specified in the outputs.

Any data collected beyond the cut-off date will not be included in the analysis. Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. For example, if the cut-off date is 15 June 2017 then an AE starting on 13 June 2017 will be reported, whereas an AE with start date on 17 June 2017 will not be reported.

All events with an event start date either before or on the cut-off date and an event end date after the cut-off date will be reported as "continuing at the cut-off date". The same rule will be applied to events starting either before or on the cut-off date and not having a documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will appear as missing in listings.

If it is required to impute an end date to be able to perform a specific analysis (e.g. end date after the cut-off date) the cut-off date needs to be imputed as an end date. The imputed date will be displayed and flagged in the listings.

17.8. SPECIFICATIONS AND ANALYSIS DATABASE

The data management of study data will be performed according to the Data Management Plan.

The study database includes the raw individual data from the eCRFs as well as RTD data. As values determined by the algorithm are not displayed on the programmer screen, data are stored in the electronic Real-Time Data (RTD) files that are loaded in the electronic Case Report Form (eCRF) in order to be extracted by the sponsor.

Research and Development Department of LivaNova will extract the RTD files based on the document MISC10244.pdf that explains the extraction and analyses method. These extracted datasets (IPTL01_LEVEA_R&D_DB_M0_M1_LV_RV_20180112.txt) will then be transferred to LivaNova Biometry. For developing Tables, Figures and Listings, analyses datasets will then be developed using the eCRF data, Dt.sas as per the methods described in this SAP and documented in the Specification Document "ADaM_metadata.xls", attached as an appendix (Appendix 2) to this SAP.

17.9. WITHDRAWAL OF INFORMED CONSENT

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a subject withdraws full consent is recorded in the eCRF.

Any data that is entered in the clinical database after the date of full consent withdrawal will be excluded from the analysis sets.

18. APPENDICES 2: ANALYSES DATASET SPECIFICATIONS

The Specification Document that describes the Analyses dataset variables is "LEVEA_Derivation_metadata.xls".