NANOSTIM STUDY

FOR A LEADLESS CARDIAC PACEMAKER SYSTEM

The LEADLESS Observational Study

Revision Date: 2017-08-22

[redacted]

Sponsor

St. Jude Medical
Clinical Studies Organization
15900 Valley View Court,
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USA

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Contents

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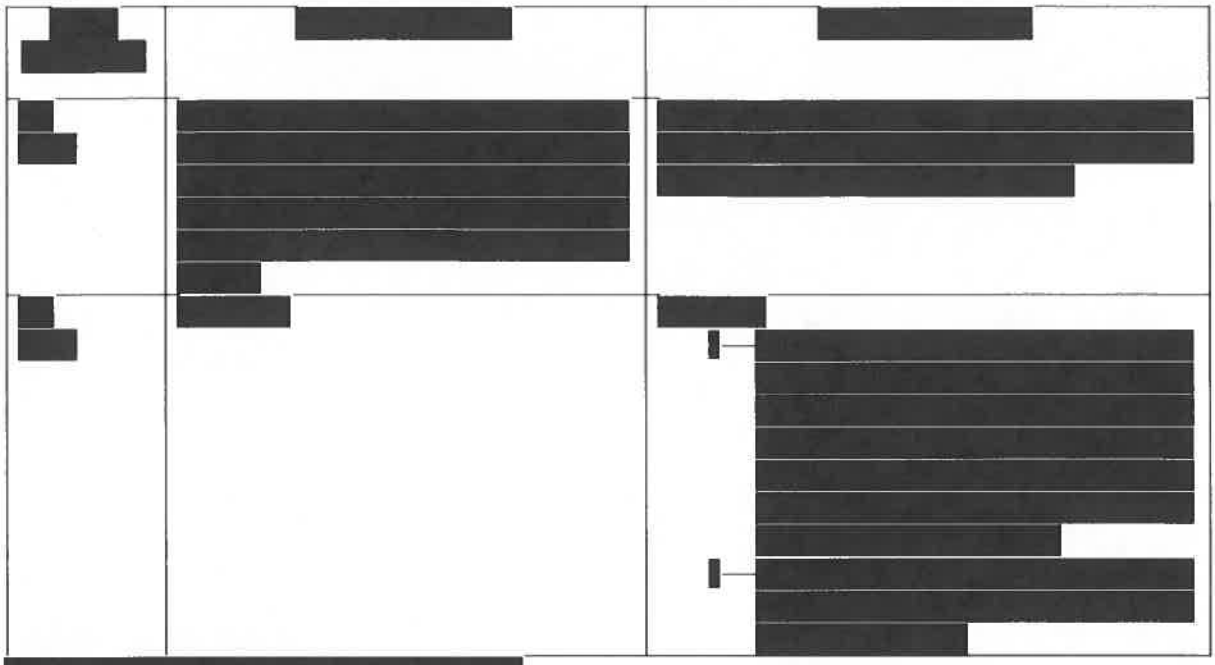

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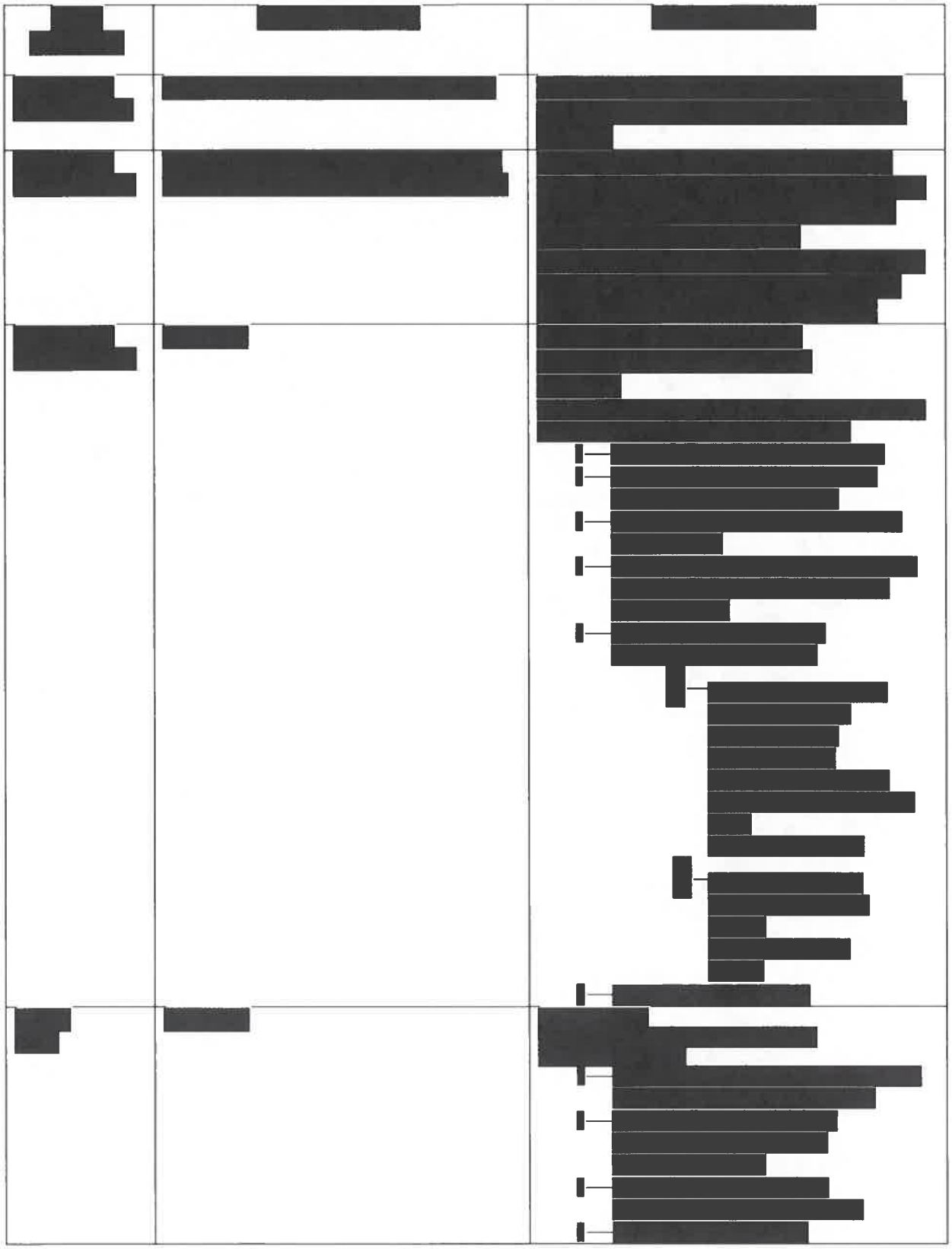

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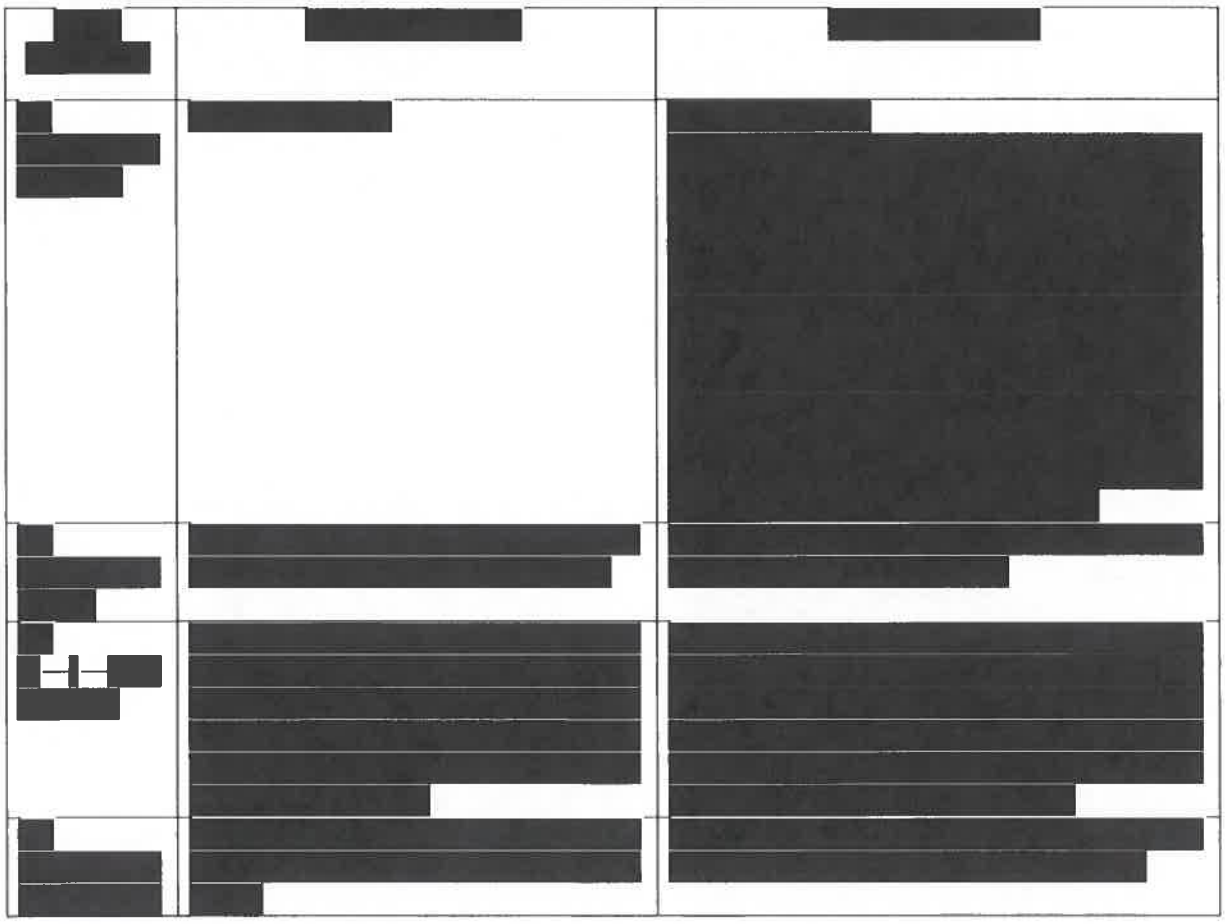

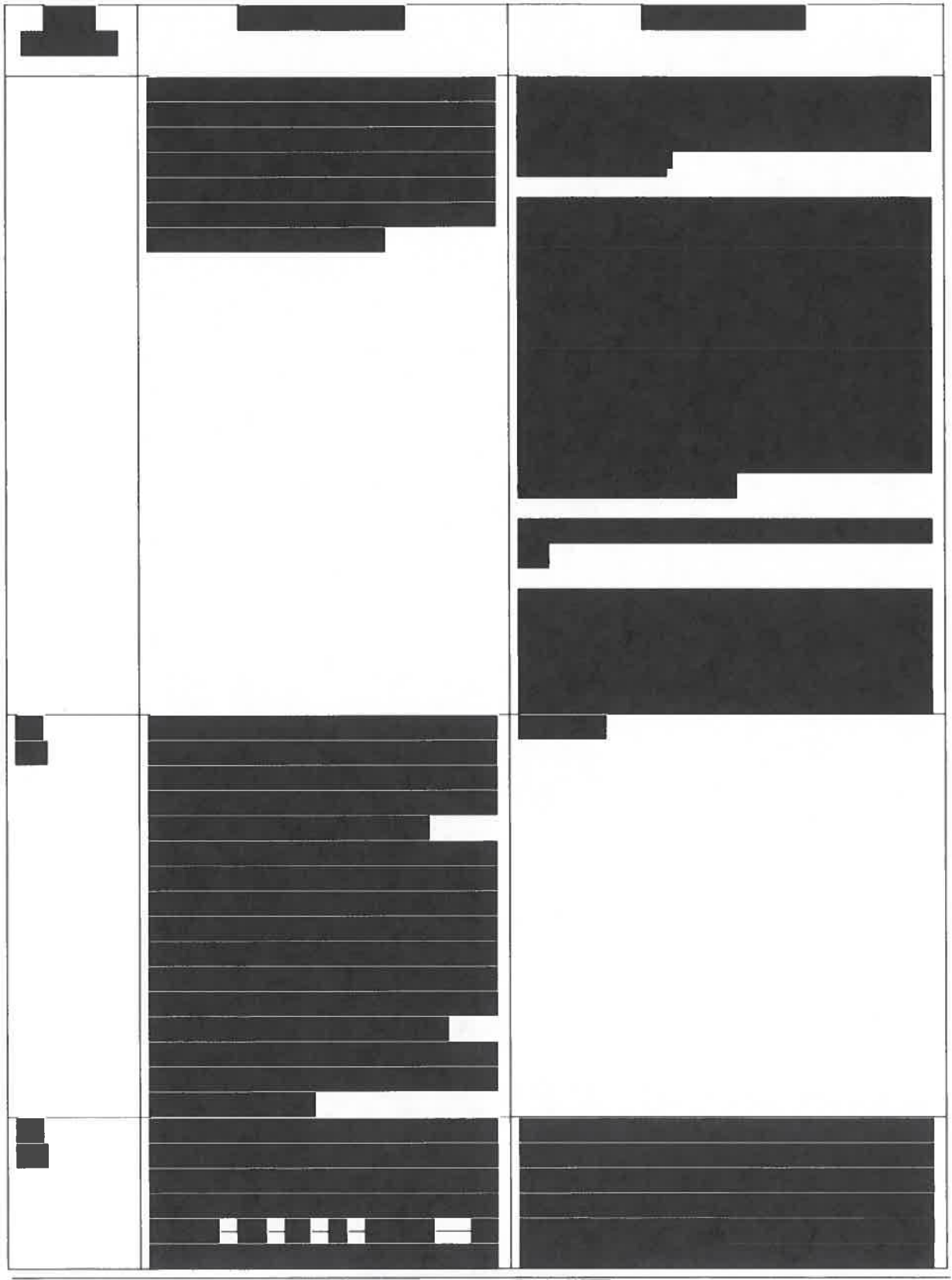

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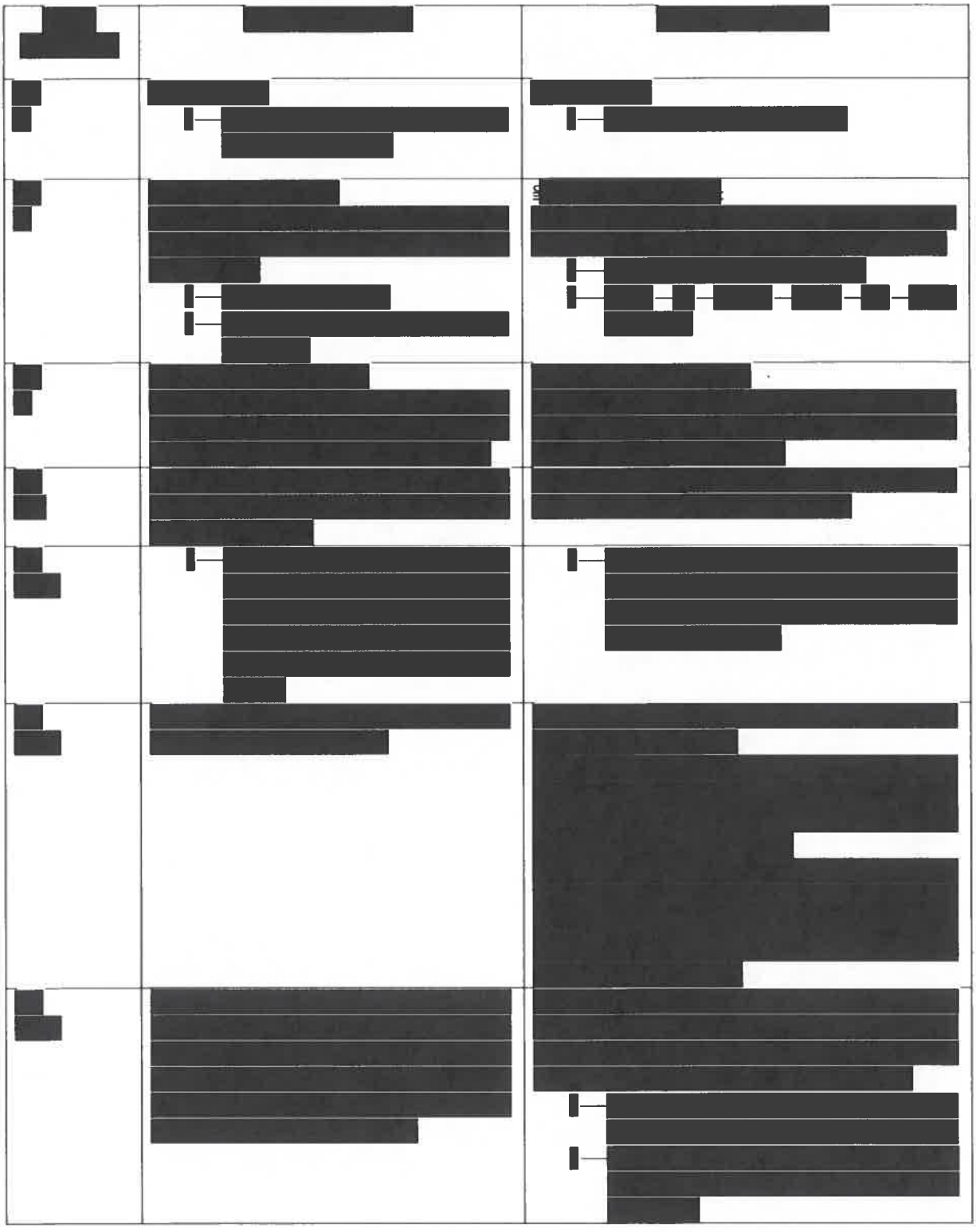

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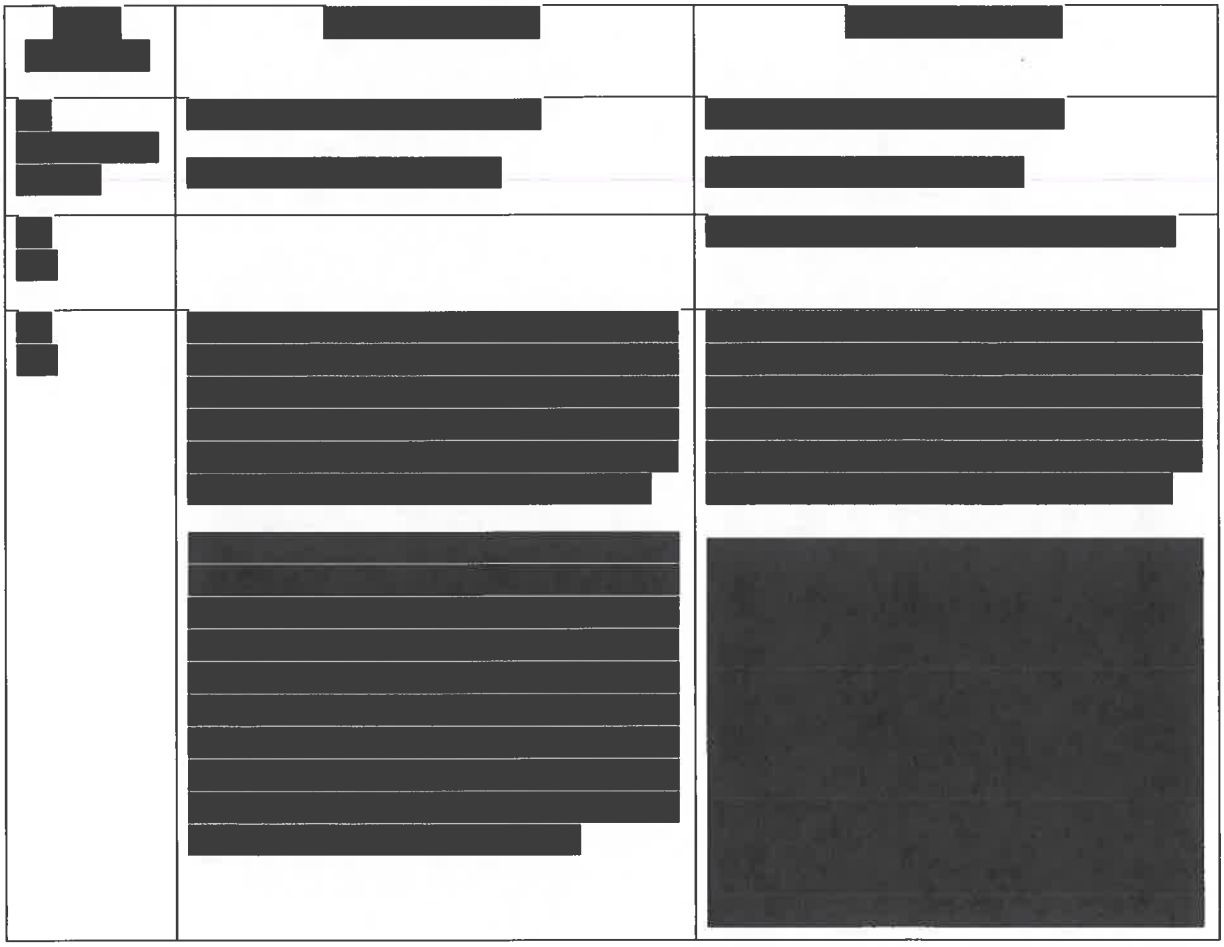

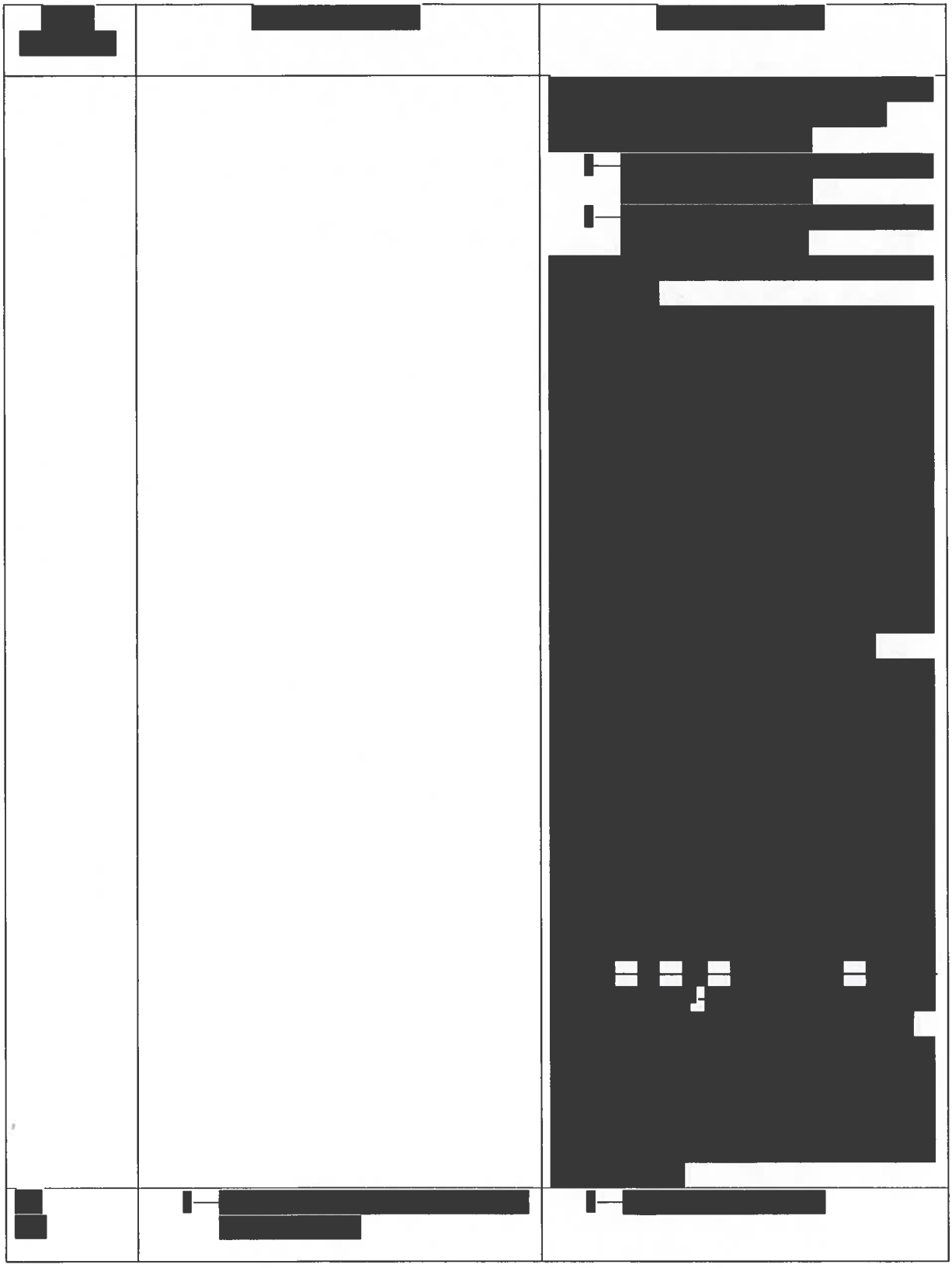

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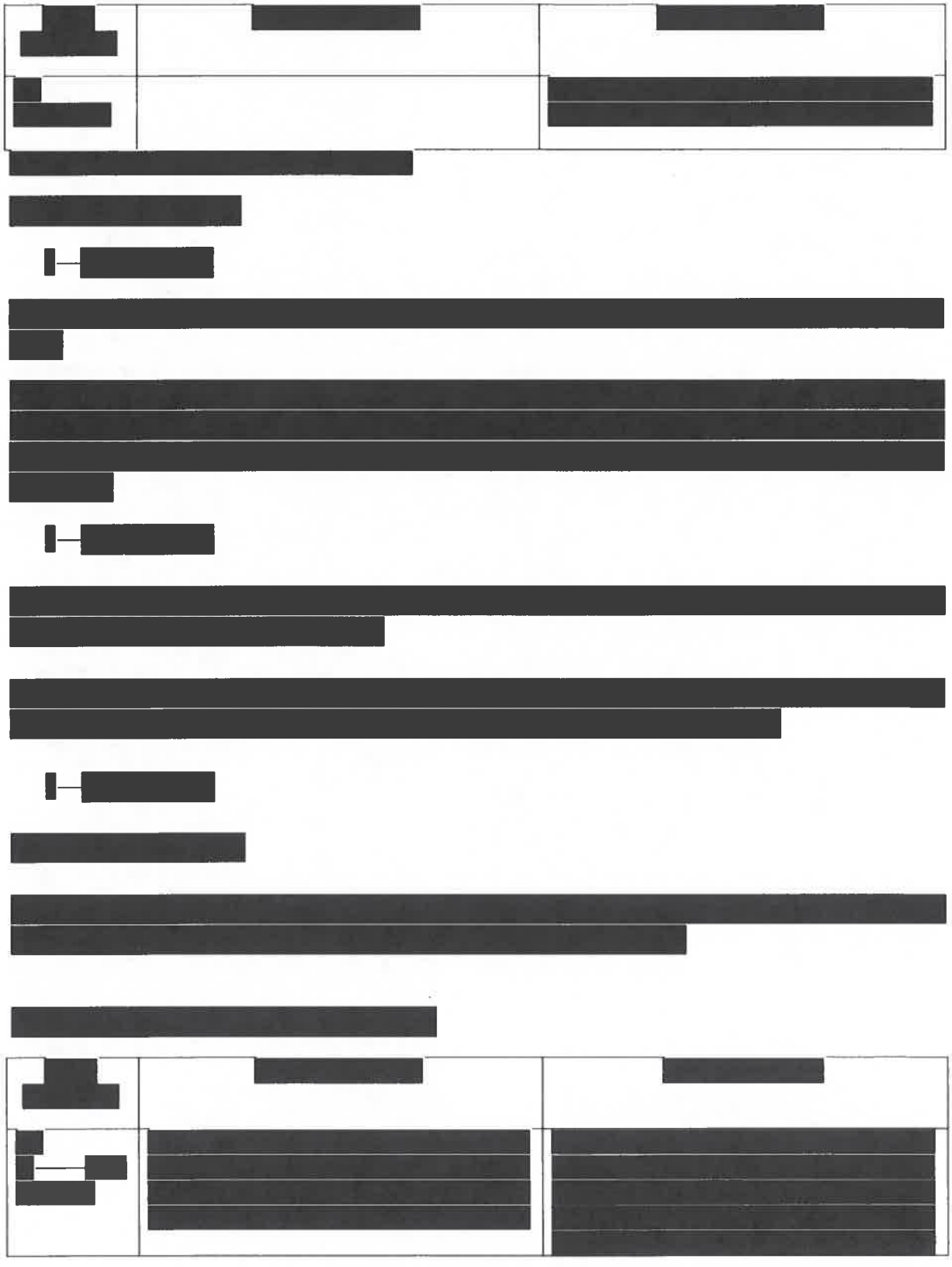

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3 STUDY SYNOPSIS

Title	Nanostim study for a leadless cardiac pacemaker system – the LEADLESS observational study
Study Device	Leadless cardiac pacemaker (LCP) system
Regulatory Classification of the Study Device	Active Implantable Medical Device (AIMD) 90/385/EEC.
Study Objective	To confirm clinical performance and safety of the Nanostim leadless cardiac pacemaker system, within its intended use and according to its instructions for use, by confirming the acceptability of identified risks and detecting emerging risks on the basis of factual evidence. A sub-set of patients enrolled in this study will be used to meet the Post Market Clinical Follow-Up (PMCF) requirement for CE mark. Once this sub-set of patients is enrolled and followed for 6 months, a report will be submitted indicating completion of this requirement.
Number of Institutions	Up to 100 study sites. [redacted]
Number of Subjects	A total of 1000 patients will be enrolled. The PMCF will be complete when data from 300 patients followed for 6 months are obtained.
Study Population	Subjects who are at least 18 years old, and who are indicated for a VVI(R) pacemaker Subjects who participated in the pre-CE mark LEADLESS study, in the Nanostim Delivery Catheter pre-CE mark study or were implanted with a Nanostim Leadless Cardiac Pacemaker within 3 months of the study start at one of the selected sites involving physician trainers and study leaders can be enrolled in this study. [redacted]

Schedule of Assessments	Enrollment, Implant, Pre-discharge, 90-day, 6-month and every 6-month follow-ups thereafter (until the last enrolled subject has completed a 5-year follow-up visit). The PMCF requirement will be met when the 300th patient has completed the 6 month follow-up visit.
Study Design	Prospective, non-randomized, single-arm, multicenter, post-market study
Primary Endpoint	The primary safety endpoint is to evaluate a 180-day complication-free rate, where a complication is defined as a serious adverse device effect (SADE).
Additional Data	- Pacing and sensing performance - All adverse events - Implant success rate - Procedure time - Time to discharge
Supplementary Endpoints	The supplementary endpoints are: - To evaluate a 90-day complication-free rate, where a complication is defined as a serious adverse device effect (SADE) - To evaluate a 5-years complication-free rate, where a complication is defined as a serious adverse device effect (SADE)
Inclusion Criteria	1. Subject must have one of the following clinical indications: • Chronic atrial fibrillation[3] with 2 or 3° AV or bifascicular bundle branch block (BBB block)[4]; or • Normal sinus rhythm with 2° or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or • Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings; and 2. Subject ≥18 years of age; and 3. Subject has life expectancy of at least one year and is a suitable candidate based on overall health and well-being; and 4. Subject is not enrolled in another clinical investigation with a treatment arm or that could confound the results of this study; and 5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and

[3] For purposes of this protocol, the term "chronic atrial fibrillation" is also defined as permanent atrial fibrillation.

[4] For purposes of this protocol, "chronic atrial fibrillation with 2 or 3° AV or BBB block" includes slow ventricular rates (with or without medication) associated with atrial fibrillation.

	6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the EC; and 7. Subject is not pregnant and does not plan on getting pregnant during the course of the study.
Exclusion Criteria	1. Known pacemaker syndrome, have retrograde VA conduction or suffer a drop in arterial blood pressure with the onset of ventricular pacing; or 2. Hypersensitivity to < 1 mg of dexamethasone sodium phosphate; or 3. Mechanical tricuspid valve prosthesis; or 4. Pre-existing ventricular pacing or defibrillation leads; or 5. Current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT); or 6. Presence of implanted vena cava filter; or 7. Evidence of thrombosis in one of the veins used for access during the procedure; or 8. Cardiovascular or peripheral vascular surgery/intervention within 30 days of enrolment;[5] or 9. Presence of implanted leadless cardiac pacemaker[6]
Enrollment	Enrollment begins when the subject provides written informed consent and agrees to participate in the clinical investigation. Eligibility for implant is based on conformance to all prospectively defined inclusion and exclusion criteria.
Anticipated Schedule	First subject enrolled: December 2013 Last subject enrolled: November 2018

[5] [redacted]

[6] This criterion is applicable only for subjects undergoing an implant. [redacted]

	Last subject visit: November 2023
Schedule of Assessments	a. For subjects with de novo Nanostim LCP implant or already implanted with a with a Nanostim LCP within 3 months of the study start at one of the selected sites Enrollment Assessments • Inclusion/exclusion criteria • Informed consent • Medical history Implant Assessments • Femoral vein assessment and access • LCP implant • LCP assessment and programming • Assess for adverse events and device deficiencies Pre-Discharge Visit • LCP assessment and programming • Assess for adverse events and device deficiencies 90-day Visit • LCP assessment and programming • Assess for adverse events and device deficiencies 6-month Visit • LCP assessment and programming • Assess for adverse events and device deficiencies Every 6-month follow-up visits thereafter (until the last enrolled subject has completed a 5-year follow-up visit) • LCP assessment and programming • Assess for adverse events and device deficiencies Optional and only for subjects with de novo Nanostim LCP implant or already implanted with a Nanostim LCP within 3 months of the study start at one of the selected sites : 24-hour Holter Recording (involving approximately 25 subjects in the study, any time after first 30 days of follow-up)
	b. For subjects who participated in the pre-CE mark LEADLESS study Enrollment Assessments • Inclusion/exclusion criteria • Informed consent • Medical history • Assess for adverse events and device deficiencies 90-day Visit (if visit occurred within 60-120 days post-implant)

	• LCP assessment and programming • Assess for adverse events and device deficiencies 6-month Visit (if visit occurred within 5-7 months post-implant) • LCP assessment and programming • Assess for adverse events and device deficiencies Every 6-month follow-up visits thereafter (until the last enrolled subject has completed a 5-year follow-up visit) • LCP assessment and programming • Assess for adverse events and device deficiencies

Table 1: Study flow and CRFs

	Pre-procedure	Procedure	Post-procedure Assessments				Additional Assessments	
CRFs	Screening & Enrollment	Implant	Pre-Discharge	90-day Follow-up Visit	6-month Follow-up Visit	Every 6-month Follow-up Visits Thereafter*	Additional Visit	24-hour Holter Recording **
Enrollment	✓							
Implant		✓						
Follow-up Visit			✓	✓	✓	✓	✓	✓
Additional CRFs (when applicable)								
Adverse Event		✓	✓	✓	✓	✓	✓	✓
Device Deficiency		✓	✓	✓	✓	✓	✓	✓
Medication Log		✓	✓	✓	✓	✓	✓	✓
Protocol Deviation		✓	✓	✓	✓	✓	✓	✓
Study Withdrawal		✓	✓	✓	✓	✓	✓	✓
System Revision			✓	✓	✓	✓	✓	✓
Out Of Service		✓	✓	✓	✓	✓	✓	✓
Death		✓	✓	✓	✓	✓	✓	✓

* To be done until the last enrolled subject has completed a 5-year follow-up visit

**To be done in approximately 25 subjects any time after first 30 days of follow-up

4 TABLE OF ABBREVIATIONS

Abbreviation	Definition	Abbreviation	Definition
2°	second degree	ESC	European Society of Cardiology
3°	third degree	FEP	Fluorinated ethylene propylene
		IB	Investigator Brochure
ABS	Acrylonitrile butadiene styrene	ICD	implantable cardioverter defibrillator
ACC	American College of Cardiology	ICF	Informed Consent Form
ACT	activated clotting time		
ADL	activities of daily living	IFU	Instructions for Use
AE	Adverse Event	INR	international normalized ratio
AHA	American Heart Association	LCP	Leadless Cardiac Pacemaker
AIMD	Active Implantable Medical Device	MRI	magnetic resonance imaging
AV	Atrioventricular	PA	pulmonary arterial
BBB	Bifascicular bundle branch	PEEK	Polyether ether ketone
		PMCF	Post Market Clinical Follow-up
CIP	Clinical Investigational Plan	PTFE	Poly tetra fluoro ethylene
CRF	Case Report Form	PtIr	Platinum Iridium
CRO	Clinical Research Organization	PVC	poly(vinyl chloride)
CRT	cardiac resynchronization therapy	RR	Rate response
EC	Ethics committee	SADE	Serious adverse device effect
ECG	Electrocardiogram	SAE	Serious Adverse Event
EP	Electrophysiology	TiN	Titanium nitride
ePTFE	expanded poly tetra fluoro ethylene		

5 IDENTIFICATION AND DESCRIPTION OF STUDY DEVICE

5.1 Device description and intended use

Nanostim has developed a leadless cardiac pacemaker (LCP) system to eliminate leads, pockets, and connectors required by conventional pacemakers and to eliminate associated complications. This concept improves patient comfort by replacing a surgical procedure with a percutaneous one (potentially permitting implantation as an outpatient) and eliminates the scar at a conventional pacemaker's pectoral implant site.

Nanostim's LCP system consists of a pacemaker and its accessories: a programmer, introducer, delivery catheter, and retrieval catheter. The accessories are not intended for use alone or with any device other than the Nanostim pacemaker. The pacemaker and all accessories, except the programmer, are single-use devices and are supplied sterile.

5.1.1 Leadless cardiac pacemaker (LCP)

Leadless **pacemaker** configuration:

[redacted]

5.1.2 Accessories

The leadless cardiac pacemaker operates with an external programmer, an introducer, a delivery catheter, and a retrieval catheter.

The **programmer** noninvasively displays the patient's electrocardiogram and the status of the implanted LCP; it sends commands to change LCP parameter settings as directed by a user. [redacted]

Currently market-approved 18F introducers incorporate tolerances that allow inner diameters to be less than 18F; therefore, Nanostim requires use of Nanostim's custom **18F introducer**. The 18F introducer operates compatibly with the pacemaker and all catheters.

The deflectable **delivery catheter system** provides means for a single operator to:

- Advance the LCP from a percutaneous access site in the groin via the femoral vein to the apex of the right ventricle,
- Position the LCP and rotate it to affix the helix,
- Undock the LCP from the delivery catheter while maintaining a connection to the LCP with a tether, to measure thresholds without force from the catheter,
- Re-dock to the catheter, unscrew and reposition the LCP if necessary for acceptable thresholds,
- Undock from the LCP, leaving it implanted, and disconnect the tether.

Apart from the docking mechanism, the delivery catheter and its control system (handle) have the same operating principle as a conventional deflectable catheter and control system.

If retrieval of an implanted LCP does not require tissue cutting or ablation, the **retrieval catheter system**, which uses either a single-loop or a triple-loop snare to engage the docking feature on the proximal end of the LCP, may be used to unscrew it and retrieve it.

Consequently, the deflectable retrieval catheter provides means for a single operator to:

- Access the LCP from a percutaneous access site in the groin through the femoral vein to the apex of the right ventricle,
- Dock to the LCP,
- Rotate it to unscrew the helix,
- Extract it through the percutaneous access in the groin.

Apart from the docking features, the retrieval catheter has the same operating principle as a conventional deflectable catheter and control system (handle).

5.1.3 Configurations and variants

In this clinical study, Nanostim includes only one variant each of the leadless pacemaker and delivery catheter, and two variants of the retrieval catheter.

Nanostim 18F Introducer Kit (Sheath + Dilator)

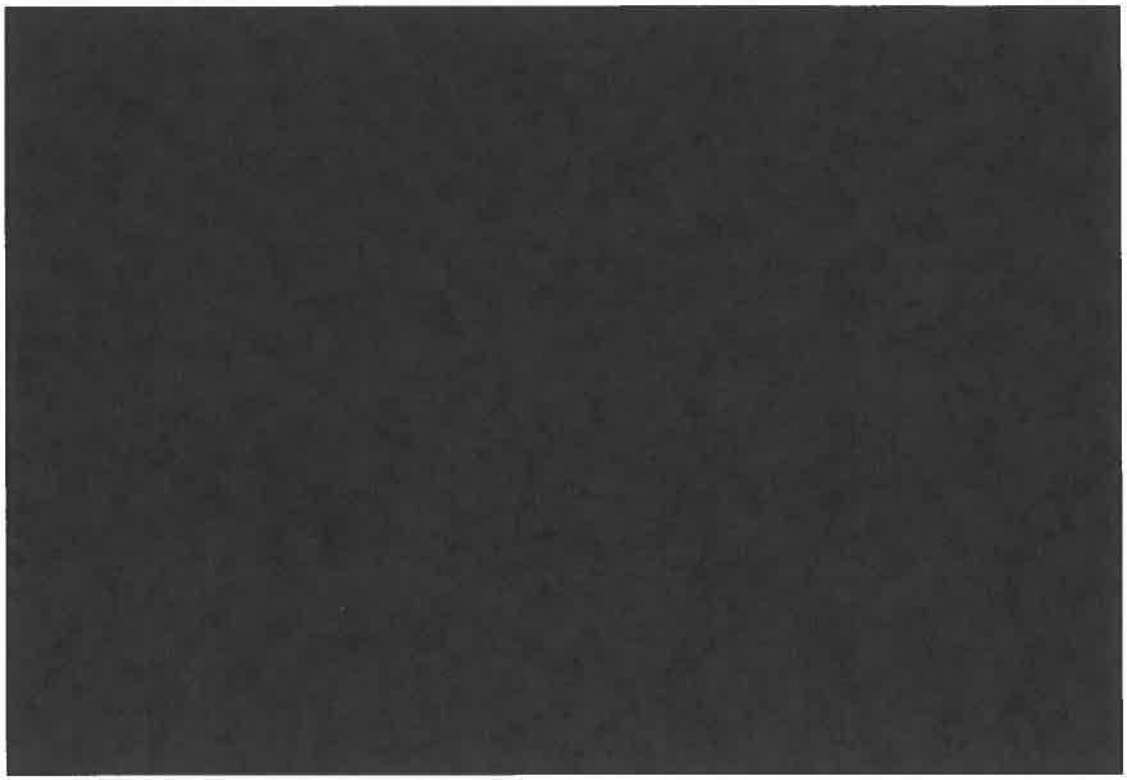
[redacted]

[redacted]

Delivery catheter system:

[redacted]

Retrieval catheter system:



5.2 Control of Devices and Shipment

Only commercially available (CE approved) shelf-stock will be used for the study.

5.3 Name or number of the model/type, including software version and accessories

[redacted]

[redacted]

6 JUSTIFICATION FOR THE STUDY DESIGN

This is a study of a CE-marked product within its approved indications, in accordance with its instructions for use. Before this study begins, the manufacturer will have demonstrated conformance of the device with essential requirements, and a positive benefit/risk balance, through pre-clinical testing and clinical evaluation, including a proper pre-market clinical investigation. However, [redacted] important information about potential residual risks can be gathered in this post-market observational study:

- [redacted]
- This study may detect rare complications that only become apparent after wider-spread use of the device, again because of the increased sample size and number of physicians implanting the system in this post-market study.
- This study may provide stability data on long-term performance of the study device, through 5 years follow-up.

Consequently, the Sponsor has designed a prospective, non-randomized, single-arm, multicenter, post-market, observational study. This study will follow 1000 patients and will be completed when the last patient reaches the 5 year follow-up visit. The design will include a study population who are at least 18 years of age and who are indicated for a VVIR pacemaker.

[redacted]

6.1 Sample size for PMCF requirement of non-inferiority of complication-free rate

The primary PMCF requirement is to establish the 180-day complication-free rate of the leadless pacemaker, compared to that of conventional pacemakers and leads, with a reduced non-inferiority margin compared to that established in the pre-market clinical investigation.

[redacted]

[redacted]

6.2 Long-term performance data

The study will observe and report the following performance data at 5 years after implant: pacing threshold, pacing impedance, R-wave amplitude and battery voltage.

6.3 Long-term safety data

The study will observe and report all adverse events and device deficiencies. For the PMCF requirement, all safety data obtained when the 300th patient has completed the 6 month follow-up visit will be reported. The supplementary endpoints of the study are complication free rate at 90 days and 5 years.

Long-term safety of the Nanostim™ LCP will be evaluated in terms of freedom from complications through 60 months of follow up. [redacted] The performance goal for the Nanostim™ LCP in this study is set to allow a small margin of 5% below that observed in the FOLLOWPACE study. This performance goal will ensure that the Nanostim™ LCP will not have an unacceptably high rate of long-term complications in comparison with transvenous pacemakers.

The hypothesis is stated as follows:

- H0: Freedom from complications through 5 years (1825 days) ≤ 75%
- Ha: Freedom from complications through 5 years (1825 days) >75%

The hypothesis will be tested at the 5% significance level (1-sided).

[redacted]

6.4 Summary of the justification for the study design

In summary, the LEADLESS observational study will gather long-term safety and performance data for the Nanostim leadless cardiac pacemaker after CE marking, within its intended use. The study is appropriately sized to evaluate residual risks of rare or delayed safety or performance issues and to confirm the positive benefit/risk balance established for the pacemaker in the premarket clinical investigation.

7 RISKS AND BENEFITS

7.1 Anticipated clinical benefits

As explained previously, before this study begins, the manufacturer will have demonstrated conformance of the study device with essential requirements, and a positive benefit/risk balance, through pre-clinical testing and clinical evaluation, including a proper pre-market clinical investigation.

Specifically, the benefits that are associated with the use of an LCP could include:

- Precise and repeatable procedure
- Percutaneous procedure (potential outpatient procedure)
- Eliminates the need for lead (no risk of lead fracture, lowers risk of infection)
- Eliminates the need for a pocket (lowers risk of infection, no need for scar and/or lump)
- Eliminates the need for connectors (eliminates connector complications)

- Conditional safe use of MRI

7.2 Anticipated adverse device effects and clinical risks

The Sponsor has documented anticipated adverse device effects in §16.8 of this observational study plan and the subject information sheet (Informed Consent Form).

Animal study results and feedback from physicians in previous clinical evaluation indicate that the delivery, implantation and retrieval procedures will not expose the subject, the physician or third parties to radiation in excess to that from implantation of a conventional single chamber pacemaker and lead.

7.3 Residual risks associated with the study device

The Sponsor applies a risk-management process compliant with current harmonized standards:

- EN ISO 13485:2012 and EN ISO 13485:2012/AC:2012, Medical devices — Quality management systems — Requirements for regulatory purposes.
- EN ISO 14971:2012, Medical devices — Application of risk management to medical devices.
- EN 62304:2006, Medical device software – Software lifecycle processes.

When implementing this risk management process, the Sponsor uses standards wherever possible: to identify hazards, hazardous situations, and appropriate risk mitigation. To ensure compliance with recent developments in European Standards, Nanostim demonstrates fulfillment of essential requirements using the latest (draft) versions of the applicable vertical and horizontal standards:

- prEN 45502-1:2010, Active implantable medical devices – Part 1: General requirements for safety, marking and information to be provided by the manufacturer
- ISO 14708-2:2012, Implants for surgery - Active implantable medical devices – Part 2: Cardiac pacemakers

In accordance with the requirements expressed therein, the Sponsor complies with other harmonized standards to manage risk in particular areas:

- EN 556-1:2001 and EN 556-1:2001/AC:2006, Sterilization of medical devices — Requirements for medical devices to be designated 'STERILE' — Part 1: Requirements for terminally sterilized medical devices.
- EN ISO 10993-1:2009, Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009). The Company also applies eight other parts of the EN ISO 10993 series.
- EN ISO 11135-1:2007, Sterilization of healthcare products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (ISO 11135-1:2007).
- EN ISO 11607-1:2009, Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems.

- EN 60601-1:2006, Medical electrical equipment – Part 1: General requirements for safety and essential performance. The Company also applies collateral standards in the EN 60601 series.

Finally, for hazards and hazardous situations not addressed by standards because of novel features in Nanostim's products, the Sponsor applies the methods of EN ISO 14971:2012 to: identify the hazards and hazardous situations; determine the probability and severity of harm considering risk mitigations applied in design, production, and information for users; asses the residual risk; and determine its acceptability for products for human use.

This observational study will complement the pre-market clinical investigation by providing longer-term data from a larger sample to confirm the positive benefit/risk balance of the pacemaker after evaluation of any residual risks related to these novel features.

7.4 Risks associated with participation in the clinical study

Although the exact complication rate is not known, adverse toxicity to the subject is not expected since the materials used in the Nanostim products are similar to those used in catheters and other pacemaker leads and pulse generators. Using standard clinical practice, Investigator will manage all anticipated complications or SAEs associated with the clinical investigation. Sponsor has detailed reporting requirements in §16.9.

Although this procedure has been successfully evaluated in a clinical investigation, not all low-level or long-term risks are known at this time. Potential procedural risks are the same as those associated with any femoral catheterization and pacemaker lead implantation procedure, including bleeding, wound healing, infection, dislodgement, thrombosis and scarring from the incision, as well as the standard risks associated with anesthesia (including an allergic reaction ranging from mild to life threatening, incomplete sedation, or heart rhythm abnormalities).

7.5 Steps that will be taken to control or mitigate the risks

Although all risks associated with this procedure and device may not be fully known at this time, the risks have been identified through clinical evaluation including an exhaustive literature search and a pre-

market clinical investigation, and represent the most up-to-date understanding of risks associated with leadless pacemaker implantation. Sponsor will employ measures throughout the course of this investigation to minimize these risks.

7.5.1 Administrative measures

- Sponsor will clearly define inclusion and exclusion criteria to ensure that only appropriate subjects are enrolled, e.g. exclusion of subjects with pulmonary arterial hypertension or lung disease.
- Investigator will obtain written informed consent.
- Sponsor will select investigation sites that have a sufficient level of clinical expertise and support to manage adverse events (AEs) that could arise and to provide appropriate alternative therapies if needed. [redacted]
- Investigator will ensure that treatment and follow-up of the subjects are consistent with current medical practices.
- Investigator will rely on medical judgment and provide institutional standard of care.
- Investigator will monitor subjects using pacemaker-programming capability to capture and monitor subject's cardiac rhythm.
- Investigator will report (S)AEs.

7.5.2 Procedure and device-related measures

- Sponsor will select Investigators who are experienced and skilled in endovascular pacemaker and lead implantation techniques.
- The device design incorporates an introducer sheath for femoral percutaneous access, which is a commonly used access site attributed with easier patient recovery than venous cut-downs.
- Catheters are under direct visual control by the attending Investigator at all times and are patterned after standard and well-established designs, similar to existing electrophysiology catheters.
- LCP incorporates an active screw-in fixation mechanism into the heart that is already familiar to physicians.
- Programming and retrieval of diagnostics are performed with an external programmer similar to existing pacing and defibrillator programmers.

7.6 Risk-to-benefit rationale

The decision to embark upon a clinical study of a medical device requires that the residual risk(s), as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure required by the study plan, be balanced against the anticipated benefits to the subjects.

The Nanostim device conforms to all applicable parts of vertical and horizontal standards that apply to cardiac pacemakers. In addition, Nanostim has considered differences between the LCP with no leads, compared to the standards that specify a pacing lead, and has addressed additional safety characteristics needed to reduce all risks to acceptable levels. Certain performance characteristics cannot be adequately measured pre-clinically and were validated in the pre-market clinical investigation. The present observational study will provide additional validation.

This observational study plan also excludes vulnerable populations (Refer to §18).

The effectiveness of cardiac pacing is well known and accepted. [5,6] The Nanostim LCP is comparable to existing VVIR therapy and the intended population for the LCP is essentially the same for approved VVIR devices. Clinical evidence already obtained addresses proof of concept of therapy and supports a positive risk-benefit balance.

Implantation of the LCP for cardiac pacing may offer certain advantages as compared to conventional pacemakers. The clinical benefits for this procedure outweigh the risks and thus provide justification for proceeding with this observational study.

8 OBJECTIVES OF THE OBSERVATIONAL STUDY

This clinical study will confirm the clinical performance and safety of the Nanostim LCP system for subjects who are indicated for a VVI(R) pacemaker by following 1000 patients for 5 years. The primary PMCF requirement for this study will be the complication-free rate at 180 days for 300 patients. Complications are defined as serious adverse device effects (SADE).

Sponsor will record and report pacing, sensing, and other performance endpoints listed in §9.1.2. Sponsor will also assess residual risks identified in the risk analysis section, and incidence of anticipated adverse events and adverse device effects listed in Table , §16.8.

9 DESIGN OF THE POST-MARKET OBSERVATIONAL STUDY

9.1 Study design

This is a prospective, non-randomized, single-arm, multicenter, post-market observational study of safety and performance.

9.1.1 Measures to be taken to minimize or avoid bias

- Each institution in this multicenter study will be using the same protocol to ensure consistent data measurement techniques among all Investigators.
- Sponsor will obtain signed Financial Disclosure statements from each participating investigator and Investigator Agreements from each participating site.
- Study endpoints are based on objective measures.

9.1.2 Primary, secondary, supplementary endpoints and additional data

- Primary Safety Endpoint: Freedom from complications (serious adverse device effect) at 180 days. Safety will be measured by reporting the complication rate, defined as SADE (§16.4).
- Supplementary Endpoints: Freedom from complications (serious adverse device effect) at 90 days and 5 years.
- Additional Data:
    - Right ventricular pacing and sensing functions (pacing threshold, R-wave amplitude, battery voltage and pacing impedance performance) at each of the study visits
    - All adverse events
    - Implant success rate,
        - Defined as the number of subjects leaving the implant procedure with an implanted and functioning LCP device, divided by the number of subjects in whom implantation is attempted.
    - Procedure time,
        - Defined as the time from delivery catheter and LCP insertion to removal of the delivery system.
    - Time to discharge,
        - Defined as the time from introducer sheath removal to discharge.

9.1.3 Equipment to be used for assessing the clinical study variables and arrangements for monitoring maintenance and calibration

Device performance is primarily measured with a Nanostim programmer and the implanted Nanostim LCP. The Nanostim programmer does not require scheduled maintenance or calibration.

9.1.4 Procedures for the replacement of subjects

- If a subject is not successfully implanted with an LCP, signs a consent but does not undergo an implant attempt, Sponsor will account for them in the final report, but will exclude them from the calculation of the primary endpoint (complication-free rate).
    - A successful implant is defined as an enrolled subject leaving the implant procedure with a functioning LCP capable of pacing and sensing.

- The sample size accounts for dropouts; therefore, neither Sponsor nor Investigator will take additional measures to replace subjects.
- Sponsor describes statistical methods in section §10.

9.2 Study device

Table 2 describes specific medical or surgical procedures involved in the use of the study device(s).

Table 2: Description of the exposure to the study device

	Medical or Surgical procedure		
Component	**Implant**	**Retrieval**	**Non-invasive follow-up**
18F Introducer kit	√	√	
LCP	√	√	√
Delivery catheter	√		
Retrieval catheter	√ (possible but unlikely)	√	
Nanostim Link Programmer and accessories	√	√	√

9.2.1 List of other medical devices or medications to be used during the clinical investigation

During the implant procedure, the physician will place a small introducer sheath in the femoral vein and inject a small amount of contrast, typically less than 10cc, to opacify and characterize the femoral access site. Likewise, the physician will place a diagnostic pigtail catheter and inject a small amount of contrast, typically less than 10cc, to opacify and characterize the right ventricular anatomy prior to LCP implantation.

9.2.2 Number of study devices to be used

Sponsor anticipates that each subject will be implanted with one LCP device in the right ventricle. In circumstances where multiple devices enter the sterile field during an implant procedure, Investigator will record and report the number of devices attempted, the reason why they were not implanted, and the final outcome.

9.3 Study population

The inclusion and exclusion criteria are consistent with recommendations of the European Society of Cardiology,[6] American College of Cardiology, American Heart Association, and the Heart Rhythm Society.[7] Additionally, Sponsor has included Investigator input.

Eligibility for implant is based on conformance to all prospectively defined inclusion and exclusion criteria:

9.3.1 Inclusion criteria

Only subjects meeting all inclusion criteria (from 1 to 7) are eligible for study participation.

1. Subject must have one of the following clinical indications:
   - ☐ Chronic atrial fibrillation[1] with 2 or 3° AV or BBB block[2]; or
   - ☐ Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or
   - ☐ Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings.
2. Subject ≥18 years of age;
3. Subject has life expectancy of at least one year and is a suitable candidate based on overall health and well-being;
4. Subject is not enrolled in another clinical investigation with a treatment arm or that could confound the results of this study;
5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams;
6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the EC;
7. Subject is not pregnant and does not plan on getting pregnant during the course of the study.

[1] For purposes of this protocol, the term "chronic atrial fibrillation" is also defined as permanent atrial fibrillation.

[2] For purposes of this protocol, "chronic atrial fibrillation with 2 or 3° AV or BBB block" includes slow ventricular rates (with or without medication) associated with atrial fibrillation.

9.3.2 Exclusion criteria

Only subjects meeting no exclusion criterion (from 1 to 9) are eligible for study participation.

1. Known pacemaker syndrome, have retrograde VA conduction or suffer a drop in arterial blood pressure with the onset of ventricular pacing;
2. Hypersensitivity to < 1 mg of dexamethasone sodium phosphate;
3. Mechanical tricuspid valve prosthesis;
4. Pre-existing ventricular pacing or defibrillation leads;
5. Current implantation of either conventional or subcutaneous implantable cardioverter defibrillator or cardiac resynchronization therapy;
6. Presence of implanted vena cava filter;
7. Evidence of thrombosis in one of the veins used for access during the procedure;
8. Cardiovascular or peripheral vascular surgery/intervention within 30 days of enrolment;[1]
9. Presence of implanted leadless cardiac pacemaker (NOTE: This criterion is applicable only for subjects undergoing an implant. [redacted]

[1] Recent cardiovascular or peripheral vascular surgery within 30 days of enrollment is defined as the following:

[redacted]

9.3.3 Study duration

The minimum length of the clinical study for each subject will be 5 years. The PMCF requirement will be met when 300 subjects have completed 6 months of follow-up. Subjects will be required to return for follow-up at 90 days (+/- 1 month), 6 months (+/- 1 month) and every 6 months thereafter (+/- 2 months) until the last enrolled subject has completed a 5-year follow-up visit.

9.3.4 Recruitment and enrollment

Candidates for this clinical study include subjects indicated for a VVI(R) pacemaker. Pre-enrollment records will include evidence of diagnosis indicating need for VVI(R) pacemaker. Preoperative screening to confirm the diagnosis is not considered part of the clinical study; however, the informed consent form will inform the subject that their medical history records used to confirm diagnosis will be incorporated into the study record.

Enrollment begins when the subject provides written informed consent and agrees to participate in the clinical study. A total of 300 subjects are needed to meet the 6-month follow-up sample size. Additional subjects will be enrolled until approximately total 1000 subjects are enrolled and everyone will be followed for at least up to 5 years post implant to document the long term performance of the system.

Patients who participated in the pre-CE mark LEADLESS study, the Nanostim Delivery Catheter pre-CE mark study or were implanted with a Nanostim Leadless Cardiac Pacemaker within 3 months of the study start at one of the selected sites involving physician trainers and study leaders can be enrolled.

[redacted]

For the pre-CE mark LEADLESS study subjects, the data collection will start after consent is obtained and will include any study related adverse event documentation after the subject exited the pre-CE mark LEADLESS study.

For the Nanostim Delivery Catheter pre-CE mark subjects, the data collection will start after consent is obtained.

For subjects who were implanted with a Nanostim Leadless Cardiac Pacemaker within 3 months of the study start at one of the selected sites involving physician trainers and study leaders, the data collection will start after consent is obtained and will include implantation procedure, pre-discharge visit and any study related events (Adverse Event, Device Deficiency, additional visit, etc.).

Additionally, 24-hour Holter data will be collected in approximately 25 subjects any time after the first 30 days of follow-up.

Sponsor anticipates that the clinical study will be completed within 6 years.

9.3.5 Subject numbering

An Identification (ID) number will identify subjects, which is a combination of the specified site number and a sequential number assigned by the sponsor. Subject initials will not be used on case report forms.

9.4 Procedures

This section provides a description of all the clinical-study-related procedures that subjects undergo during the clinical study. Table 1 lists a summary of scheduled assessments. The clinical-study-related procedures do not require additional radiation compared to a traditional VVIR lead implant and conform to standard of care for pacemaker subject management with the exception of femoral vein access instead of cephalic, axillary, or subclavian vein access.

Sponsor representatives may assist the Investigator in assessing pacemaker performance (for example pacing and sensing performance), downloading diagnostic information, and programming pacemaker parameters. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

9.4.1 Enrollment assessment

The Investigator will not start any study-specific procedures or alterations of subject care until the informed consent process has been completed and Investigator obtains a signed Informed Consent Form. To determine eligibility, some screening procedures may be necessary. If any of these tests do not fall within the Investigator's standard clinical practice, they will be required for subjects to be enrolled in the clinical study.

During this visit, investigation team will collect medical history data.

In addition:

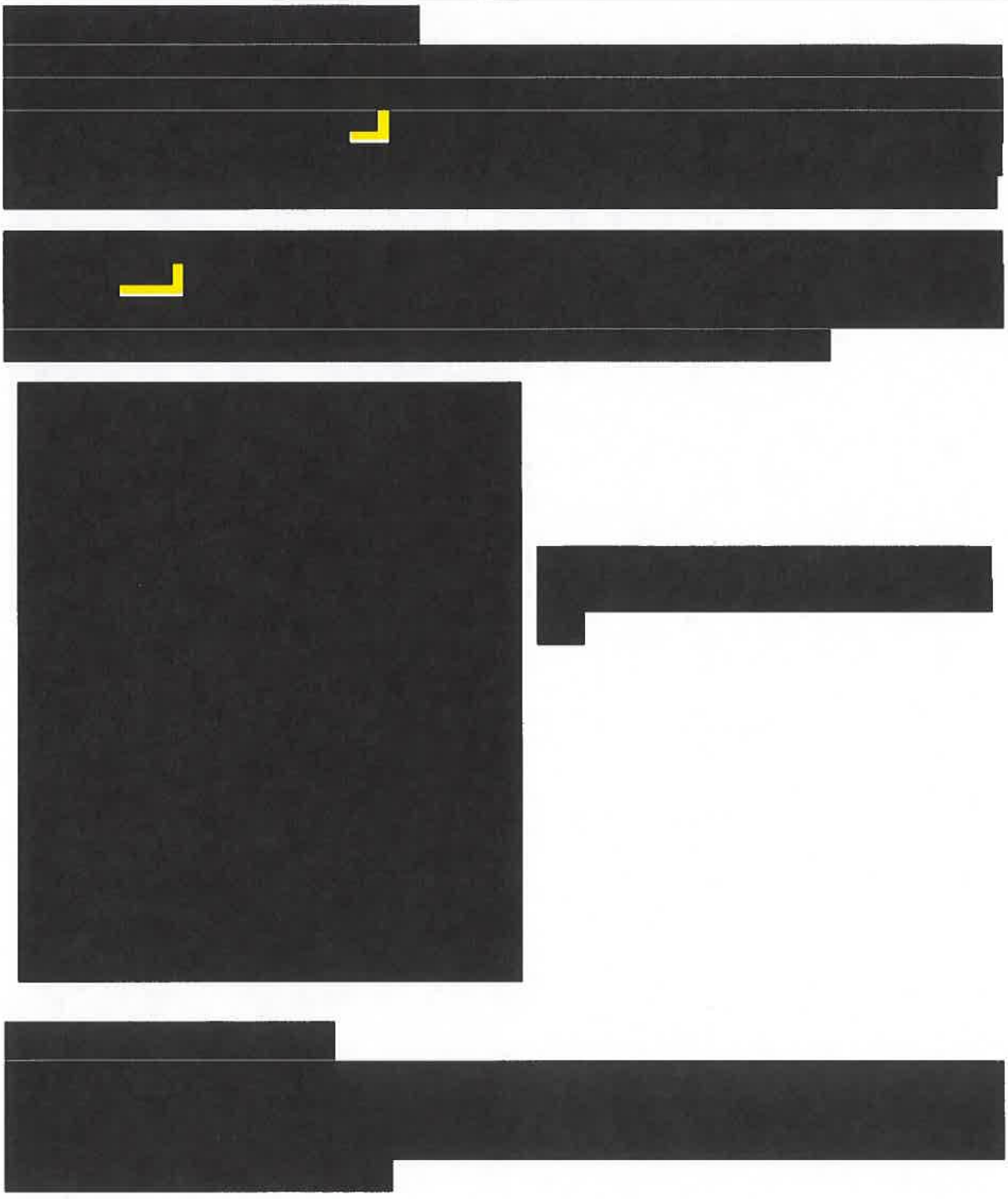
- For subjects who were previously implanted with a Nanostim LCP at one of the selected sites involving physician trainers and study leaders, investigation team will collect implant procedure data, pre-discharge data and any study related events (Adverse Event, Device Deficiency, additional visit, etc.).
- For pre-CE mark LEADLESS study subjects, investigation team will collect any study related adverse events.

9.4.2 Implant procedure

Medications

Investigator will administer all medications per hospital standard of care for pacemaker implant and femoral venous catheterization procedures. Anticoagulation medications may be used with the implantation of the LCP per physician's discretion. Investigator will record all medications given during procedure on subject's medical record.

[redacted]



[redacted]

9.4.3 Post-procedure assessments

This section does not apply to subjects who were previously implanted with a Nanostim LCP.

The follow-up period is sufficient to demonstrate performance. Additionally, during this follow-up period, Sponsor will identify and assess any risks associated with adverse device effects (ADEs). Subjects will continue with follow-up visits consistent with the institution's standard of care for pacemakers. Table 1 lists the schedule of assessments.

Investigator will assess enrolled subjects, who have an LCP implant attempted but whose implant procedure cannot be completed, for AEs occurring up to 30 days post implant attempt.

Investigator will report any subjects who require LCP revision after implantation.

- If the subject has the Nanostim™ LCP removed at any time during the study, and the subject will receive another Nanostim LCP, the investigator will continue following the patient in the study.
- If the subject has the Nanostim™ LCP removed or deactivated at any time during the study, and the subject will not receive a replacement Nanostim™ LCP, the investigator will assess the subject for AEs occurring up to 30 days post revision.

Access-site management during hospital stay

Investigator will manage access sites per standard of care. Investigator will assess and document any post-procedural access-site bleeding event based on the following grading system.

ACCESS-SITE OOZING: Superficial bleeding of a cutaneous or subcutaneous origin characterized by diffuse localized bleeding and controlled with minimal care (e.g., application of manual pressure, application of sandbag).

ACCESS-SITE HEMATOMA: A localized collection of extravasated blood in subcutaneous tissue at the access site that does not require intervention. A metric ruler should be used to measure the widest portion of the hematoma.

ACCESS-SITE HEMATOMA REQUIRING INTERVENTION: A localized collection of extravasated blood in subcutaneous tissue at the access site that is considered life threatening and requires emergency wound exploration (e.g., acutely expanding hematoma, acute leg pain/numbness/swelling) and/or prolongation of hospital stay.

ACCESS-SITE RE-BLEEDING: Localized bleeding at the access site that occurs after hospital discharge. These bleeds are typically associated with an event (e.g., fall, attempted suture removal, physical activity).

Pre-Discharge Visit

Investigator will use medical judgment and provide institutional standard of care for post-pacemaker-implant monitoring.

During this visit, investigation team will:

- Assess for adverse events, device deficiencies and deviations to this observational study plan,
- Check pacing capture threshold, R-wave amplitude, pacing impedance, and battery voltage,
- Adjust programmable parameters of LCP, as needed

9.4.4 90-day follow-up visit (within 60-120 days post-implant)

This section may apply to subjects who were previously implanted with a Nanostim LCP if the visit is within the 90-day visit window (within 60-120 days post implant).

All subjects will return to the implant center at the investigation site for a 90-day follow-up visit. During this visit, investigation team will:

- Assess for adverse events, device deficiencies and deviations to this observational study plan,
- Check pacing capture threshold, R-wave amplitude, pacing impedance, and battery voltage,
- Adjust programmable parameters of LCP, as needed, and

9.4.5 6-month follow-up visit (within 5-7 months post-implant)

This section may apply to subjects who were previously implanted with a Nanostim LCP if the visit occurred within the 6-month visit window (within 5-7 months post implant).

All subjects will return to the implant center at the investigation site for a 6-month follow-up visit. During this visit, investigation team will:

- Assess for adverse events, device deficiencies and deviations to this observational study plan,
- Check pacing capture threshold, R-wave amplitude, pacing impedance, and battery voltage, and
- Adjust programmable parameters of LCP, as needed.

9.4.6 Every 6-month follow-up visits thereafter (until the last enrolled subject has completed a 5 year visit)

All subjects will return to the implant center at the investigation site every 6 months for a follow-up visit after the 6-month follow-up visit until the last enrolled subject has completed a 5 year visit. During this visit, investigation team will:

- Assess for adverse events, device deficiencies and deviations to this observational study plan,
- Check pacing capture threshold, R-wave amplitude, pacing impedance, and battery voltage, and
- Adjust programmable parameters of LCP, as needed.

9.4.7 Holter data collection visit

This section does not apply to subjects who were already implanted with a Nanostim LCP.

24-hour Holter data will be collected in approximately 25 subjects, any time after the first 30 days of follow-up.

9.4.8 Additional visit(s)

If a subject returns to the implant center at the investigation site for a clinically-warranted unscheduled visit, investigation team will:

- Assess for adverse events, device deficiencies and deviations to this observational study plan,
- Check pacing capture threshold, R-wave amplitude, pacing impedance, and battery voltage, and
- Adjust programmable parameters of LCP, as needed.

9.5 Monitoring plan

On site-monitoring shall be performed during the clinical investigation in order to guarantee adherence to all applicable regulations, the clinical investigation plan and the signed Clinical Study Agreement. By monitoring, the Sponsor can also verify the accuracy of data collected on the accompanying Case Report Forms (CRFs: electronic or paper) throughout the duration of the study.

Monitoring is necessary to ensure adequate protection of the rights and safety of human subjects involved in the clinical investigation and the quality and integrity of the data obtained during the investigation. The sponsor will at the same time assess the investigational site and study team on staffing and facilities to ensure the investigation can continue in a safe and effective fashion.

During the monitoring visits, data reported on the CRF shall be reviewed as specified in the monitoring plan. (Refer to section 9.5.2).

9.5.1 Designated Monitors

Only monitors qualified by education, training and experience, which have been trained on the Clinical Investigation Plan, CRF content, Monitoring Plan, relevant requirements and informed consent process will be allowed to perform monitoring activities during this clinical investigation. The monitor's qualifications and training will be documented by the sponsor. A list of monitors is available upon request.

9.5.2 Monitoring Plan

Prior to the start of the site monitoring activities for this clinical investigation, a project specific Monitoring Plan (MP) will be created and will be available upon request.

At a minimum, the Monitoring Plan will include the following:

- Required activities
- Frequency of monitoring visits
- Visit Requirements
- Procedures for securing site compliance
- Monitoring report content and timelines
- Close-out procedures

The Monitoring Plan may be updated as appropriate. All revisions will be tracked.

9.5.3 Competent Authority (CA) Inspections

The investigator and/or delegate should contact the sponsor immediately upon notification of a CA inspection at the site. A clinical monitor will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access shall permit authorized CA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the investigation, shall permit authorized CA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the investigation.

An investigator shall permit authorized CA employees to inspect and copy records that identify subjects, upon notice that CA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC/IRB have not been submitted or are incomplete, inaccurate, false or misleading.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical design, method and analytical procedures, sample size, level of significance and power

Refer to § 6.1 for a discussion of statistical design for the primary objective.

The sample size also permits application of the normal approximation to distributions of means. This enables the clinical study to provide confidence intervals derived from sample means and standard deviations of performance parameters (§9.1.2).

Table 2: Summary of the objectives and the analytical procedures of the clinical investigation

Objective	Type of objective	Clinical testing
180-day Complication-free rate (CFR)	Primary safety	Confidence Interval
5-year CFR	Supplementary	Confidence Interval
Implant-success rate (ISR)	Additional data	Descriptive statistics
LCP Performance[1]	Additional data	Descriptive statistics at all visits

Descriptive statistics will provide mean, standard deviation, and a two-sided 90 % confidence interval.

10.2 Lost-to-follow-up, dropouts and subgroup analysis

Refer to § 19.1 for lost-to-follow-up procedure. [redacted]

[1] LCP performance includes capture thresholds, R-wave amplitude, battery voltage and pacing impedance.

[redacted]

Investigator will provide data on subjects, in whom an implant was attempted but who were unable to have a device implanted, to record and report any SAEs during and up to 30 days from the attempt. [redacted]

Reasons for inability to implant the LCP device include, but are not limited to, tortuous anatomy not allowing passage of the LCP, inability to advance introducer into the femoral vein or straight portion of the inferior vena cava, or vessel size not allowing insertion of 18F introducer. Subjects who are enrolled but never undergo an implant attempt will be followed for 30 days post attempt by the Investigator and will be reported by the Sponsor.

10.3 Termination on statistical grounds

Criteria for terminating the clinical study on statistical grounds are not needed because this is a study of a CE-marked device within its intended use, for which existing vigilance regulations and procedures provide adequate safeguards.

At any time, any subject may terminate his or her participation as provided in their informed consent, and any investigator may terminate his or her participation as provided in their investigator agreement.

11 DATA MANAGEMENT

Data collected through an EDC system or paper case report forms will be available in a central database. Sponsor will review all incoming data to identify inconsistent or missing data as well as any adverse events. Sponsor will promptly address any data issues with the Investigator. Sponsor will establish quality assurance procedures to ensure that complete, accurate and timely data are submitted, that observational study plan requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigator will maintain all source documents as required by the observational study plan, including laboratory results, supporting medical records, and signed Informed Consent forms. Sponsor and/or monitor will use source documents during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

11.1 Data retention

Sponsor and Investigator will maintain the clinical investigation documents for a minimal period of five (5) years after the clinical investigation is completed, or longer depending on national requirements. They will take measures to prevent accidental or premature destruction of these documents and ensure these

are filed in a secure place. Investigator or Sponsor may transfer custody of records to another person or party and document the transfer at the investigation site, or at the Sponsor's facility.

11.2 Clinical quality assurance and quality control

Sponsor has integrated clinical quality assurance and quality control in the Sponsor's quality system. Quality assurance and quality control principles will apply to the processes of the clinical study. Sponsor will:

- Implement and maintain written clinical quality procedures to ensure that the clinical study is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with ISO 14155:2011, the observational study plan, any subsequent amendment(s), and any other applicable standards and regulatory requirements,
- Maintain records to document the compliance of all parties involved in the clinical study,
- Ensure that the auditing requirements are met, and
- Justify and document significant exceptions to the requirements of ISO 14155:2011.

12 AMENDMENTS TO AND DEVIATIONS FROM THE OBSERVATIONAL STUDY PLAN

Sponsor and Investigator will conduct this clinical investigation in accordance with the Observational Study plan, ISO 14155, and all applicable regulatory requirements associated with the Active Implantable Medical Device Directive, including transpositions of the Directive into national law.

Investigator will not deviate from the Observational Study plan without prior written confirmation by Sponsor, or their designee, except as required in a medical emergency. In medical emergencies, Sponsor does not require prior confirmation for protocol deviations, but Investigator will notify Sponsor within 5 days of the incident and will notify the EC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to Sponsor who will analyze them and assess their significance.

Routine monitoring will assess Investigator compliance to the protocol as described in §9.5.

Investigator must not modify the Observational Study plan without the prior and written permission from Sponsor. Sponsor and Investigator will agree to all amendments made to the Observational Study plan. Sponsor and/or Investigator will record a justification for the amendments. If Observational Study plan changes affect the scientific soundness of the clinical investigation, or affect the health, welfare, safety and rights of subjects, Investigator and/or Sponsor will obtain written approval by the Investigator's EC, and Competent Authority, when applicable, before implementing changes. If changes are merely administrative in nature, Investigator will notify their EC.

13 DEVICE ACCOUNTABILITY

This is an observational study to confirm positive benefit/risk balance in a CE-marked device within its intended use; consequently it does not require special device accountability procedures for the post-market clinical study. The manufacturer's standard operating procedures for shipping and receiving will suffice.

14 STATEMENTS OF COMPLIANCE

1. Sponsor and Investigator will conduct the clinical study in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
2. Sponsor and Investigator will comply with applicable parts of ISO 14155:2011 and any regional or national regulations, as appropriate.
3. Investigator will not begin the clinic study until Investigator obtains the required written approval or favorable opinion from the EC or regulatory authority, if appropriate.
4. Investigator will follow any additional requirements imposed by the EC or regulatory authority, if appropriate.
5. Sponsor will provide insurance for subjects.

15 INFORMED CONSENT PROCESS

Investigators will not ask subjects to sign the Informed Consent Form (ICF) until the clinical study has been fully approved by the institution's EC, and the Sponsor or their CRO representative has received and reviewed the specific EC-approved ICF. When Investigator has determined the eligibility of a specific subject to enter the clinical study, Investigator, or designee, will discuss and explain the clinical investigation with the subject. Investigator will provide ICF to the subject. Subject will read the ICF, and Investigator will answer any questions. Investigator will provide ample time to the subject to decide on his/her participation and obtain a signed ICF from the subject before performing the implant procedure or any protocol-specific tests. Investigator will provide subjects with a copy of their signed ICF. Investigator will provide new information to new and existing subjects.

Investigator will maintain a copy of the EC-approved ICF along with a copy of each subject's signed Informed Consent Form in a designated study file.

16 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Using the specific signs, symptoms or abnormal laboratory values, Investigator will classify and report adverse events. Investigator will use medical diagnosis if no signs, symptoms or abnormal laboratory values are identified. A Clinical Event Committee (CEC) will adjudicate all device or procedure-related adverse events in the study.

16.1 Adverse events (AE)

An **adverse event** is 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.

- This definition includes events related to the investigational medical device.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational devices.

A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions, such as atrial fibrillation that are present prior to study entry and do not worsen during the clinical investigation will not be considered an AE. An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it:

- Results in subject's withdrawal from the clinical investigation by the Investigator;
- Is associated with a serious adverse event;
- Is associated with clinical signs or symptoms;
- Is considered by the physician to be of clinical significance or resulting in a serious deterioration in subject health status.

16.2 Serious adverse events (SAE)

A **serious** adverse event is an 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-patient 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, or
    5. Malignant Tumor
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

Sponsor understands that medical interventions may involve IV and IM drug delivery and surgical interventions involve an invasive procedure. Non-invasive means such as oral drugs or device re-programming do not meet the criteria for medical or surgical intervention.

16.3 Adverse device effect (ADE)

An **adverse device effect** is an adverse event related to the use of a study medical device.

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.

This definition includes any event resulting from use error or from intentional misuse of the study medical device.

16.4 Serious adverse device effect (SADE)

A **serious adverse device effect** is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. SADE will include significant loss of device function even if the Investigator chooses not to intervene to correct it.

16.5 Anticipated serious adverse device effect (ASADE)

Anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

16.6 Unanticipated serious adverse device effect (USADE)

An **unanticipated serious adverse device effect** is a 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.

16.7 Device deficiency

A **device deficiency** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency is detected or suspected, Investigator will document it on the Device Deficiency Form and return the device according to the instructions provided in the Investigator's study binder(s).

Investigator will report device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

a. If either suitable action had not been taken,
b. If intervention had not been made, or
c. If circumstances had been less fortunate.

A **malfunction** is a failure of a study medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP.

A **use error** is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

Refer to reporting requirements in §16.9.

16.8 List of foreseeable adverse events and anticipated adverse device effects

The table below provides a list (non-exhaustive a potential adverse events, device related, procedure related and/or subject condition related.

-Next Page-

Table 3: List of foreseeable adverse events and anticipated adverse device effects

Air embolism	Interruption of desired pacemaker function due to electrical interference, either electromyogenic or electromagnetic
Angina pectoris	Keloid formation
Arterial puncture	Loss of normal device function due to battery failure or component malfunction
Bladder puncture	Muscle and nerve stimulation
Blunted or poor sensor response	Myocardial damage
Body rejection phenomena	Myocardial infarction
Bowel penetration	Myocardial irritability
Cardiac arrhythmias	Oversensing
Cardiac dissection	Pacemaker syndrome
Cardiac perforation	Palpitations
Cardiac tamponade	Pericardial effusion
Chronic nerve damage	Pericardial rub
Damage to vessels	Pericarditis
Device dislodgment	Phrenic nerve/diaphragm muscle stimulation
Dizziness	Premature battery depletion
	Programmer/software anomaly
Dyspnea	Pseudoaneurysm formation
Embolism	Psoas abscess
Endocarditis	
Excessive Bleeding	Septic arthritis
Exit block	Seroma
Failure to capture/loss of capture	Syncope
Femoral nerve injury with resulting paresthesias	Threshold elevation
Fluid accumulation	Thromboemboli
Hematoma formation, including retroperitoneal hematoma/hemorrhage	Thrombosis
High impedance	Undersensing
Inability to interrogate or program due to programmer or device malfunction	Valve damage
Induced ventricular ectopy or arrhythmias	Venous occlusion
Infection, local at access site, or system	Venous perforation
Insufficient cardiac output	Ventricular ectopy
Intermittent capture	Ventricular tachycardia

16.9 Handling and reporting of adverse events

Investigator will report *"to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports"* **[ISO 14155 § 9.8 b]**.

All Serious Adverse Events and all Adverse Device Effects (serious or non-serious) are to be documented and reported to the sponsor within a maximum period of 72 calendar hours after becoming aware of the event. Investigator will send reports via EDC, email or fax.

Sponsor contact information:

[redacted]

Non-Serious Adverse Events documentation and reporting are limited to cardiovascular events. These events are to be reported to the sponsor within maximum 10 calendar days after becoming aware of the event.

Where possible, Investigator will return the device involved in the deficiency to Sponsor for analysis.

Investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, severity, relationship to the investigational device and/or procedure, required interventions, duration, and outcome. Investigator will monitor all AEs until they are resolved, determined to be a chronic condition at the last follow-up visit or the subject is lost to follow-up. Investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, intensity, outcome or causality within 72 calendar hours. Investigator will make all efforts to provide source documentation related to the event (e.g. hospitalization report, medical report, etc.).

In the event of subject death, Investigator will make reasonable effort to obtain a copy of the autopsy report and/or death summary. Investigator will determine the cause of death and its relationship to the investigational device; Investigator will record results on the Adverse Event Form. Investigator will include copies of an autopsy report, if available, and/or a death summary with this form.

Investigator is responsible for reporting all SAEs or SADEs to the EC, according to national regulations and EC requirements. Investigator will forward a copy of this report to Sponsor and file in site regulatory binder.

Sponsor is responsible for classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in line with ISO 14155:2011 and regulatory requirements.

Sponsor will assure reporting of all SAEs to the Competent Authorities in accordance with European Medical Devices Directives and all applicable national regulations.

17 DATA AND SAFETY MONITORING BOARD

Data Safety Monitoring Board will be responsible for review of data on a periodic basis until 300 patients needed for the PMCF requirements complete 6 months of follow-up.

18 VULNERABLE POPULATION

"Clinical investigations shall be conducted in vulnerable populations only when they cannot be carried out in non-vulnerable populations and shall follow the additional EC procedures where applicable. These clinical investigations shall be designed specifically to address health problems that occur in the vulnerable population, and offer the possibility of direct health-related benefit to the vulnerable population." § 4.6 ISO 14155:2011

Sponsor and Investigator will exclude vulnerable populations from this clinical study.

19 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL STUDY

19.1 Subject lost to follow-up

Investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects; two of these attempts should include attempting to contact subject via registered mail. Investigator will document the date and type of attempted communication. Investigator will complete and sign the Study Withdrawal Form when a subject is lost to follow-up.

19.2 Subject withdrawals and discontinuation

Subjects have the right to withdraw from the clinical study at any time and for any reason without prejudice to their future medical care by the study team or study site. Investigator will ask reason for their withdrawal. Investigator will record all information regarding the subject discontinuation.

A subject may be withdrawn from the clinical study for the following reasons:

- Subjects may choose to withdraw from the clinical study under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;
- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the subject if treatment is continued;
- Development of any intercurrent illness(es), infection or condition(s) that might interfere with the CIP;
- Non-compliance with the clinical study procedures deemed by the Investigator to be sufficient to cause discontinuation;

- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

Investigator will treat all subjects discontinued from the study due to an unanticipated adverse reaction, directly related to the study, until the reaction resolves.

Investigator will not replace subjects who have withdrawn from the clinical study if they have received study treatment. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

19.3 Early termination of clinical study

Both the Sponsor and Investigator reserve the right to terminate the clinical study at any time.

20 PUBLICATION POLICY

The results of the clinical investigation will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor (if applicable).

If such a Publication Agreement is not signed by both parties as a separate agreement but as part of an overall Clinical Trial Agreement, the publication policy should be part of such a Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

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