Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads

NAVIGATE X4 Clinical Study

CLINICAL PROTOCOL

NAVIGATE X4 IDE#: G130222

Sponsored By

Boston Scientific, CRM
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St. Paul, MN 55112

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Revision History

Revision Number	Release Date	Change, Including Reason for Change
Version AB	**December 17, 2013**	**Changes to implement FDA feedback and clarifications**
Version AA	**August 1, 2013**	**Original Version, not released for study use**

2. PROTOCOL SYNOPSIS

<table>
<tr><th colspan="2">NAVIGATE X4 Clinical Study
Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads</th></tr>
<tr><td>Objective(s)</td><td>The objective of the NAVIGATE X4 Clinical Study is to gather data to establish the safety, performance and effectiveness of the ACUITY™ X4 quadripolar coronary venous leads and the RELIANCE 4-FRONT™ ventricular defibrillation leads to satisfy FDA requirements for pre-market submission. Additionally, data from this study will be used to support post-market approval requirements for the ACUITY X4 and RELIANCE 4-FRONT leads.</td></tr>
<tr><td>Test Leads</td><td>ACUITY™ X4 Quadripolar Coronary Venous Leads
RELIANCE 4-FRONT™ Ventricular Defibrillation Leads</td></tr>
<tr><td>Model Numbers of Leads included in NAVIGATE X4</td><td>
ACUITY™ X4 Quadripolar Coronary Venous Leads*
<table>
<tr><th rowspan="3">Tip Configuration</th><th rowspan="3">Electrode Spacing</th><th colspan="2">Length</th></tr>
<tr><th>86cm</th><th>95cm</th></tr>
<tr><th colspan="2">Model Number</th></tr>
<tr><td>Straight</td><td>Even</td><td>4671</td><td>4672</td></tr>
<tr><td rowspan="2">Spiral</td><td>Short tip</td><td>4674</td><td>4675</td></tr>
<tr><td>Long tip</td><td>4677</td><td>4678</td></tr>
</table>
*ACUITY X4 will be investigational in the US during a portion of the study

RELIANCE 4-FRONT™ Ventricular Defibrillation Leads*
<table>
<tr><th rowspan="3">Lead Fixation Type</th><th rowspan="3">Lead Type</th><th colspan="3">Lead Length</th></tr>
<tr><th>59cm</th><th>64cm</th><th>70cm</th></tr>
<tr><th colspan="3">Model Number</th></tr>
<tr><td rowspan="3">Active</td><td>Dual Coil</td><td>0675</td><td>0676</td><td>NA</td></tr>
<tr><td>Single Coil G</td><td>0692</td><td>0693</td><td>0657</td></tr>
<tr><td>Dual Coil G</td><td>0695</td><td>0696</td><td>0658</td></tr>
<tr><td rowspan="3">Passive</td><td>Dual Coil</td><td>0665</td><td>0636</td><td>NA</td></tr>
<tr><td>Single Coil G</td><td>0682</td><td>0683</td><td>0654</td></tr>
<tr><td>Dual Coil G</td><td>0685</td><td>0686</td><td>0655</td></tr>
</table>
*RELIANCE 4-FRONT will be investigational in the US during a portion of the study
G= Gore ePTFE (expanded-polytetrafluoroethylene) covered coil(s)
</td></tr>
</table>

NAVIGATE X4 Clinical Study

Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads

Model Numbers of BSC X4 CRT-Ds that may be used in NAVIGATE X4

Boston Scientific (BSC) X4 CRT-Ds

Device Name	US Model Numbers	International Model Numbers	Description of Port RV/ LV/ RA
AUTOGEN™ X4	G166*	G177	DF1/ IS4/ IS1
AUTOGEN™ X4	G168*	G179	DF4/ IS4/ IS1
DYNAGEN™ X4	G156	G156	DF1/ IS4/ IS1
DYNAGEN™ X4	G158	G158	DF4/ IS4/ IS1
INOGEN™ X4	G146	G146	DF1/ IS4/ IS1
INOGEN™ X4	G148	G148	DF4/ IS4/ IS1
ORIGEN™ X4	G056	G056	DF1/ IS4/ IS1
ORIGEN™ X4	G058	G058	DF4/ IS4/ IS1

*AUTOGEN X4 will be investigational in the US during a portion of the study

Additional Devices

3140 Zoom Wireless Transmitter (ZWT)

3141 USB Cable Accessory

2909 Multiple Application Utility (MAU)

NOTE: the 3140 ZWT, and 2909 MAU are investigational devices in the USA only and may become approved for commercial use during the study

Study Design

The NAVIGATE X4 Clinical Study is a prospective, non-randomized, multi-center, single-arm, global clinical study.

Planned Number of Subjects

NAVIGATE X4 is a clinical study that will support data collection for ACUITY X4 quadripolar coronary venous leads and RELIANCE 4-FRONT ventricular defibrillation leads. [redacted]

NAVIGATE X4 Clinical Study **Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads**	
	
Planned Number of Centers/ Countries	Up to 125 centers located in the United States, Israel, and Canada.
ACUITY X4 Primary Safety Endpoint	Lead-related Complication-Free Rate from Implant through 6 Months Post-Implant (
ACUITY X4 Primary Effectiveness Endpoint 1	Pacing capture thresholds in the programmed configuration, evaluated at 3 months post-implant (Responders are defined as subjects with PCT ≤ 2.5 V in the programmed configuration.
ACUITY X4 Primary Effectiveness Endpoint 2	Pacing capture thresholds (PCT) in the proximal zone (E2, E3, or E4) for analyzed at 3 Months post-implant.
ACUITY X4 Secondary Effectiveness Endpoint 1	Sensed amplitude in the programmed configuration, analyzed at 3 Months post-implant
ACUITY X4 Secondary Effectiveness Endpoint 2	Pacing impedances in the programmed configuration, analyzed at 3 months post-implant.
RELIANCE 4-FRONT Primary Safety Endpoint 1	Lead-related Complication-Free Rate (CFR) from Implant through 3 Months Post-Implant
RELIANCE 4-FRONT Primary Safety Endpoint 2	Lead-related Complication-Free Rate from 3 Months through 24 Months Post-Implant

NAVIGATE X4 Clinical Study **Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads**	
RELIANCE 4-FRONT Secondary Safety Endpoint	Detection of Ventricular Tachyarrhythmia's (VT/VF) within 30 days of implant
RELIANCE 4-FRONT Primary Effectiveness Endpoint	Pacing Thresholds at 0.5 ms pulse width, analyzed at 3 Months Post-Implant
RELIANCE 4-FRONT Secondary Effectiveness Endpoint 1	Sensed Amplitude, analyzed at 3 Months Post-Implant
RELIANCE 4-FRONT Secondary Effectiveness Endpoint 2	Pacing Impedance, analyzed at 3 Months Post-Implant
RELIANCE 4-FRONT Secondary Effectiveness Endpoint 3	Ventricular Tachyarrhythmia (VT/VF) Shock Conversion, analyzed within 30 days of implant
Follow-up Schedule	Study procedures or clinic visits will occur at the following time periods. - Enrollment Visit (less than or equal to 30 days from implant procedure) - Implant Procedure (Day 0; all future follow ups based on this date) - Pre-Discharge Clinic Visit (3 – 72 hours) - 3 Month Clinic Visit (91 ± 21 days) - 6 Month Clinic Visit (182 ± 21 days) - 12 Month Clinic Visit (365 ± 45 days) - 18 Month Clinic Visit (547 ± 45 days) - 24 Month Clinic Visit (730 ± 45 days) - 30 Month Clinic Visit (913 ± 45 days) - 36 Month Clinic Visit (1095 ± 45 days) - 42 Month Clinic Visit (1278 ± 45 days) - 48 Month Clinic Visit (1461 ± 45 days) - 54 Month Clinic Visit (1643 ± 45 days) - 60 Month Clinic Visit (1826 ± 45 days) The study will be considered complete after all subjects have completed the 5 year follow-up.

NAVIGATE X4 Clinical Study Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads	
	[redacted]
Study Duration	Study completion is anticipated in 2019. Primary endpoint completion and US regulatory submission for ACUITY X4 is anticipated after all subjects [redacted] have completed the 6-Month follow-up visit. For RELIANCE 4-FRONT, primary endpoint completion and US regulatory submission is anticipated after all subjects implanted with the RELIANCE 4-FRONT lead have completed the 24-Month follow-up visit. All study required visits will be completed during clinic visits.
Key Inclusion Criteria	• Subjects indicated for a CRT-D that fulfill one of the following 5 criteria[1]: 1. Subject with LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and a NYHA class II, III or ambulatory IV symptoms on GDMT* 2. Subject with LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT* 3. Subject with LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ ambulatory class IV symptoms on GDMT* 4. Subject with atrial fibrillation and LVEF less than or equal to 35% on GDMT* if a) the subject requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT 5. Subject on GDMT* who have LVEF less than or equal to 35% and are undergoing new device placement with anticipated requirement for significant (>40%) ventricular pacing *GDMT= Guideline-directed medical therapy (formerly known as optimal pharmaceutical therapy (OPT)), represents optimal medical therapy as defined by ACCF/ AHA guideline-recommended therapies (primarily Class I) • Subject is intended to receive the ACUITY X4 LV lead and RELIANCE 4-FRONT RV lead (optional in Study Phase 1) and BSC CRT-D with quad header as their initial (*de novo*) cardiac implants • Subject is willing and capable of providing informed consent (which can include the use of a legally authorized representative (LAR) for documentation of informed consent) and participating in all testing associated with this investigation at an approved center and at the intervals defined by this protocol

NAVIGATE X4 Clinical Study Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads	
	• Subject is age 18 or above, or of legal age to give informed consent specific to state and national law
Key Exclusion Criteria	• Subject has a known or suspected sensitivity to dexamethasone acetate (DXA) • Subject has a mechanical tricuspid heart valve • Subject is enrolled in any other concurrent study, with the exception of local mandatory governmental registries and observational studies/registries* that are not in conflict and do not affect the following: o Schedule of procedures for the Study (i.e. should not cause additional or missed visits); o Study outcome (i.e. involve medications that could affect the heart rate of the subject); o Conduct of the Study per GCP/ ISO 14155:2011/ 21 CFR 812, local regulations • Subject is currently on the active heart transplant list • Subject has a documented life expectancy of less than twelve months • Women of childbearing potential who are or might be pregnant at the time of study enrollment or CRT-D System implant (method of assessment upon physician's discretion) • Subjects currently requiring chronic dialysis * Sponsors of such studies/registries should be informed and Boston Scientific must be informed by the investigator about the parallel conduct of these projects in the subject and of the project's basic nature. The decision if a desired mandatory governmental registry or observational study/ registry is in conflict with this exclusion criterion is up to the enrolling investigator.

Statistical Methods	
Endpoint Hypotheses and Statistical Test Methods	[redacted]

Sample Size Justification	The overall study sample size is in accordance with current FDA requirements for lead approval. All endpoints for each lead (ACUITY X4 and RELIANCE 4-FRONT) are adequately powered to at least 80%.

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3. INTRODUCTION

Cardiac resynchronization therapy (CRT) has demonstrated immediate acute hemodynamic improvement[2, 3] as well as long-term improvement in functional capacity, quality of life, symptomatic heart failure severity and mortality.[2, 4-7] Typically, CRT is administered by means of bi-ventricular pacing in which right ventricular (RV) pacing is delivered through standard endocardial leads and left ventricular (LV) stimulation is achieved through a coronary venous lead within a branch of the coronary sinus (CS) or great cardiac vein. LV stimulation using coronary venous leads and endocardial defibrillation and pace/sense leads are used as an integral part of an implantable cardiac resynchronization therapy (CRT-D) system. CRT-Ds are intended to provide ventricular anti-tachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. A lead provides the insulated electrical conductor between the implantable pulse generator (PG) and the cardiac tissue and conducts sensed intrinsic cardiac electrical signals to the PG and delivers to the heart, as necessary, artificial stimulation from the PG. The lead is a complex mechanical structure that has to withstand biodegradation in the environment of the body, repetitive flexural cycles of the heart, and compressive and tensile forces in the extravascular space. To be successful, LV leads must not only be able to navigate through the vasculature to a potential target site, but they must also achieve good contact with viable myocardium, allow repositioning if needed, and then remain in a stable position over time to allow therapy delivery. Maintaining myocardial contact and stable positioning are often achieved by pre-shaping the distal tip of a lead or adding a feature to wedge it within the vessel.[8-12] Further, design requirements may be related to ease of implant handling, fluoroscopic visualization, diameter of the lead body, durability to last beyond the replacement of several PGs, performance to stimulate the cardiac tissue with low energy, ability to reliably sense intrinsic cardiac activity, ability to defibrillate, and a design with consideration of future lead extraction.

In recent years there has been considerable focus on lead malfunctions.[13-19] As a result of this, Boston Scientific has continued to leverage reliable lead design attributes from currently marketed products and refine its design controls process to create validated, *in vitro* test methods. These test methods have informed design changes that will produce a more robust lead. There has also been an increase in regulatory requirements for testing of the leads both in pre-market clinical trials and post-market follow-up studies.

Boston Scientific has leveraged previous design attributes, conducted *in vivo* pre-clinical studies, completed an acute human study (LILAC), and evaluated the design with validated, *in vitro* bench tests to ensure the safety and efficacy of its next generation LV lead. The ACUITY™ X4 lead family utilizes many attributes of the current EASYTRAK 2 and ACUITY Spiral coronary venous leads (i.e. tine and spiral fixation, IROX coated electrodes, steroid, tapered distal tip, and lead body materials). The notable design changes for ACUITY X4 from the predecessor leads is the addition of cable conductors, an IS4 terminal and four electrodes to make a quadripolar lead.

Although it may seem that the somewhat tortuous path of a lead within the coronary venous system should be enough to hold it in place, reported experiences with lead dislodgement suggest that some type of passive fixation is needed to counter heart motion and retrograde blood flow.[8] Historically, the mode of fixation has been a passive one although active fixation coronary venous leads are currently available. These active fixation leads have positive results in terms of

lead dislodgment[20-22] although extraction may be a difficult. Some implanters have reported success with stent implantation in order to stabilize the LV.[23-25] While others have reported implanting an over-the-wire LV lead, inserting a stiff stylet into the lead, and then cutting the stylet with no lead dislocations observed in 35 patients after 12 months of follow-up.[26] Risk factors for lead dislodgments may include large lead-to-vein diameter mismatch, rapid myocardial motion and superficial insertion.[27]

Phrenic nerve stimulation (PNS) is a known complication of resynchronization therapy and may hinder LV pacing. PNS has been detected in approximately 30% of patients treated with CRT.[28] The ability of implanted devices to allow flexible LV pacing configurations is a useful feature for preventing PNS.[28-30] This essentially allows "electronic repositioning" and limits the need for surgical lead revision. The optimal LV pacing configuration should be determined on the basis of individual patient testing and can lead to successful and effective outcomes of CRT therapy.[31] Recent developments in LV lead design have resulted in quadripolar leads to allow more choices in lead placement and programming capability.

Boston Scientific has also designed, bench tested, and animal tested a new defibrillation lead based on the ENDOTAK RELIANCE family of defibrillation leads, called RELIANCE 4-FRONT™. The RELIANCE family of leads has a proven track record of performance over the last ten years. RELIANCE 4-FRONT maintains many of the robust design aspects from the RELIANCE lead family (i.e. fixation, electrode surface area and spacing, lead body configuration, insulation thickness and materials). The notable design change for RELIANCE 4-FRONT from the predecessor lead is a reduced lead body diameter, enabled by a new high voltage conductor cable. Additional dimensional changes were made to some components in the lead to accommodate the smaller lead body size; while insulation thicknesses did not change from the RELIANCE lead family for abrasion and dielectric strength performance. The outside diameter allows all leads in the family to fit through an 8 French introducer when implanted without a retained guidewire. The lead includes an active fixation method (identical to the RELIANCE lead family) using an extendable/ retractable helix and a passive fixation method using tines.

The objective of this study is to obtain US regulatory approval of both ACUITY X4 and RELIANCE 4-FRONT by gathering data to establish the safety, performance and effectiveness of the ACUITY X4 Quadripolar Coronary Venous Leads and RELIANCE 4-FRONT Defibrillation leads. Subjects enrolled into this clinical study will be indicated for a CRT-D and will be implanted with a RELIANCE 4-FRONT lead. Because the RELIANCE 4-FRONT leads have the same indications for use as existing defibrillation leads, the clinical study will seek no new indications for use. The endpoints related to RELIANCE 4-FRONT lead performance include the ability to stimulate cardiac tissue, the ability to record intrinsic cardiac activity, and pacing lead impedance in the normal range. Subject safety will be monitored with attention focused on lead-related complications throughout the study. Subjects who enroll into the NAVIGATE X4 Clinical Study, will be consented for 5 years of follow-up evaluation. The data will contribute to the total sample size necessary to satisfy post-market regulatory data collection requirements.

4. DEVICE DESCRIPTION

The devices included in the NAVIGATE X4 Clinical Study are the ACUITY X4 LV lead (description included in Section 4.3), RELIANCE 4-FRONT RV lead (description included in Section 4.5), AUTOGEN X4 CRT-D (description included in Section 4.7), or market-released BSC CRT-D with quad header, 2868 PRM software application, 2909 multiple application utility (MAU), and the 3140 Zoom Wireless Transmitter (ZWT) that provides Medical Implantable Communication Services (MICS) telemetry with the market approved 3120 Zoom LATITUDE programmer/recorder/monitor (PRM). Devices to be used in the study that are investigational are summarized below.

4.1. *Programming System*

The programming system consists of the 3120 Zoom LATITUDE PRM, 2909 MAU, 2868 software application, and the 3140 ZWT with a 3141 USB cable. The 3120 Zoom LATITUDE PRM is approved for commercial use. The 2909 MAU, 2868 software application and 3140 ZWT will all be investigational in the US at the start of the NAVIGATE X4 Study.

At the start of the NAVIGATE X4 Study a dedicated clinical 3120 Zoom LATITUDE PRM and investigational ZWT will be provided to US centers after they are approved to enroll. The dedicated clinical 3120 Zoom LATITUDE PRM, used in the US, will contain the investigational 2909 MAU and 2868 software application and will be labeled for use only with an AUTOGEN X4 PG. **Do not interrogate any market released PGs with the dedicated clinical 3120 Zoom LATITUDE PRM.** During the course of the NAVIGATE X4 Study, the 2909 MAU, 2868 software application, and the 3140 ZWT may become approved for commercial use in the US. If this occurs:

- there will be no change to the protocol;
- the dedicated clinical 3120 Zoom LATITUDE PRM will be returned to BSC after the market approved 2909 MAU and 2868 software version are available;
- the 3140 ZWT labeled as investigational will be returned to BSC after the market approved device is available; and
- the 3140 ZWT and 3120 Zoom LATITUDE PRM will no longer be tracked as an investigational device through this study after the investigational device/ equipment accountability log is reconciled (see Section 15).

4.1.1. 2909 Multiple Application Utility (MAU)

The 2909 MAU Version 9.02 is the operational system used to launch software applications on the 3120 Zoom LATITUDE PRM, including the 2868 software application.

4.1.2. 2868 PRM Software Application

The Model 2868 PRM Software Application is used to support the communication with the BSC X4 CRT-Ds in conjunction with the 2909 MAU.

NOTE: the version of the 2909 MAU or 2868 software application may be updated during the study. If this occurs, investigational centers will be notified of the new software version(s) and a BSC representative will update the software on the PRM.

A programmer key (dongle) is required to interrogate the investigational (US versions) AUTOGEN X4 model G166-100 and G168-100 CRT-Ds. A programmer key is only available for use by a Boston Scientific representative. Therefore a BSC representative will need to be present any time the investigational AUTOGEN X4 CRT-D (G166-100, G168-100) is interrogated. **This will continue to be a requirement during the NAVIGATE X4 Study (in the US) until the AUTOGEN X4 device is FDA-approved.**

During the course of the NAVIGATE X4 Study, the AUTOGEN X4 CRT-D may become approved for commercial use. If this occurs:

- there will be no change to the protocol and
- the programmer key will no longer be required to interrogate the device

Note: Subjects in NAVIGATE X4 who are implanted with a BSC X4 CRT-D other than AUTOGEN X4 (INOGEN X4, ORIGEN X4, DYNAGEN X4 once they are commercially available) or international subjects implanted with devices outside the US, will not need to have their devices interrogated using the programmer key.

4.2. *Zoom Wireless Transmitter*

The ZWT, model 3140, provides radio frequency (RF) telemetry using the MICS band. The ZWT is connected to a 3120 Zoom LATITUDE PRM using the 3141 USB cable.

MICS telemetry operates over a range of 402 MHz – 405 MHz using 10 channels. The ZWT is available for use with the 2868 software application. Inductive telemetry is also available to interrogate, program and communicate with the Boston Scientific X4 CRT-Ds using the wired telemetry wand.

4.3. *ACUITY X4 Quadripolar Coronary Venous LV Lead*

The Boston Scientific ACUITY X4 quadripolar coronary venous leads are intended for chronic left ventricular pacing and sensing. These steroid-eluting leads have an over-the-wire design and an IS4[1] four-pole connector. A variety of pace/sense configurations are possible with the four distal, IROX-coated electrodes that can function as cathodes (all four electrodes) or anodes (all except E1, the most distal electrode) when used with a compatible pulse generator. ACUITY X4 leads are available in three tip configuration designs (straight tip, short tip spiral, long tip spiral)—intended to provide choices for a variety of patient anatomies. A small diameter, atraumatic tip with small diameter silicone distal sections on all lead models is designed to track into tortuous vasculature.

1. IS4 refers to the international standard ISO 27186:2010.

See Figure 1 below for a picture of the ACUITY X4 leads as well as the layout of the electrodes on the lead. Refer to Section 25.1 for a more detailed description of the ACUITY X4 leads.

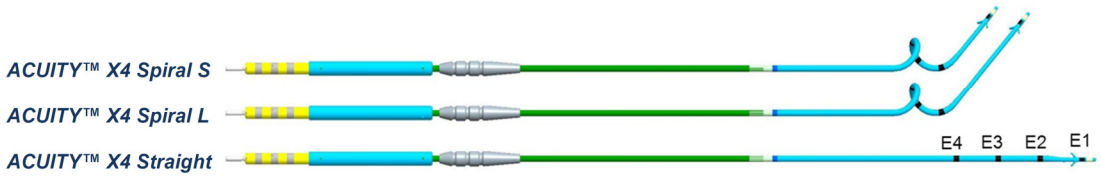


Figure 1: ACUITY X4 Leads and Electrode Placement

Note: Nomenclature of electrodes on the lead (E1, E2, E3, E4) is an industry standard. The corresponding nomenclature on the BSC PRM is as follows:

- E1: LV Tip 1
- E2: LV Ring 2
- E3: LV Ring 3
- E4: LV Ring 4

4.4. *ACUITY X4 Quadripolar Coronary Venous Lead and Associated Accessory Models*

Table 1 includes the model numbers and lead lengths of the ACUITY X4 leads.

Table 1: ACUITY X4 Lead Models

Tip Configuration	Electrode Spacing	Length	
		86cm	95cm
		Model Number	
Straight	Even	4671	4672
Spiral	Short tip	4674	4675
	Long tip	4677	4678

Table 2 includes the accessories used with ACUITY X4 leads.

Table 2: ACUITY X4 Lead Accessories

Component	Model Number**
ACUITY X4 Flushing Tool*	4604
ACUITY X4 Connector Tool*	4625
Vein Pick*	6541
Quadripolar Connector Lead Cap	7007
Slit Suture Sleeve (optional)	4603

*These accessories packaged with ACUITY X4 leads (model numbers do not apply)

**Model numbers to order components as accessories

4.5. *RELIANCE 4-FRONT Ventricular Defibrillation Leads*

The RELIANCE 4-FRONT lead is designed for right-side heart applications within the ventricle, atrium, and superior vena cava. It is equipped with one quadripolar connector defined by ISO 27186 [Active Implantable medical devices – Four-pole connector system for implantable cardiac rhythm management devices], which contains both high and low voltage connections. RELIANCE 4-FRONT is intended for permanent sensing, pacing, and defibrillation when used with a compatible Implantable Cardioverter Defibrillator (ICD) (not for the NAVIGATE X4 Study) or Cardiac Resynchronization Therapy Defibrillator (CRT-D). For the purpose of the

NAVIGATE X4 Clinical Study, only commercially available or investigational BSC CRT-Ds with quad headers are allowed. The RELIANCE 4-FRONT lead is designed to be placed into the venous anatomy through an 8 Fr introducer.

Refer to Section 25.2 for a more detailed description of this lead.

4.6. *RELIANCE 4-FRONT Lead and Associated Accessory Models*

Table 3 contains the model numbers and lead lengths of the RELIANCE 4-FRONT Leads.

Table 3: RELIANCE 4-FRONT Lead Models

		Lead Length		
		59cm	64cm	70cm
Lead Fixation Type	**Lead Type**	**Model Number**		
Active	Dual Coil	0675	0676	NA
	Single Coil G	0692	0693	0657
	Dual Coil G	0695	0696	0658
Passive	Dual Coil	0665	0636	NA
	Single Coil G	0682	0683	0654
	Dual Coil G	0685	0686	0655

G= Gore ePTFE (expanded-polytetrafluoroethylene) covered coil(s)

Table 4 includes the accessories used with RELIANCE 4-FRONT Leads.

Table 4: RELIANCE 4-FRONT Accessories

Component	Accessory Model Number
Soft Straight Stylets	6601 (59cm), 6964 (70cm), 6972 (64cm)
Firm Straight Stylets	6602 (59cm), 6963 (70 cm), 6971 (64cm)
Vein Pick	6541
Quadripolar Connector Lead Cap	7007
EZ-4 Connector Tool	7001
Tunneler Accessory Kit	6888
Quadripolar Lead Pulling Tip	7006
Slit Suture Sleeve (optional)	6403

4.7. *Boston Scientific X4 CRT-Ds*

Boston Scientific's new family of CRT-D devices include several models as listed in Table 5. They provide a variety of therapies including:

- Ventricular tachyarrhythmia therapy used to treat rhythms associated with sudden cardiac death such as VT and VF,

- CRT which treats heart failure by resynchronizing ventricular contractions through biventricular electrical stimulation, and
- Bradycardia pacing, including adaptive rate pacing, to detect and treat bradyarrhythmias and to provide cardiac rate support after defibrillation therapy.

This family of CRT-Ds includes models that are not intended to accept quadripolar coronary venous LV leads (they accept IS-1 or LV-1 coronary venous leads). Those models in the family that are compatible with quadripolar coronary venous leads include "X4" in their name and are listed in Table 5 below. As a family of devices, they will be referred to as BSC X4 CRT-Ds. All models in the BSC X4 CRT-D family may be implanted in NAVIGATE X4 once commercially available. The AUTOGEN X4 CRT-D devices are investigational in the US until approval of AUTOGEN (non X4) CRT-D devices; they may be used in NAVIGATE X4 while investigational. Therefore, there is one algorithm included in the AUTOGEN X4 that is investigational in the US until approval of AUTOGEN; it is PaceSafe, which is described further in Section 4.7.1.

Table 5: Boston Scientific X4 CRT-Ds Allowed in NAVIGATE X4

Device Name	US Model Numbers	International Model Numbers	Description of Port RV/ LV/ RA
AUTOGEN™ X4	G166*	G177	DF1/ IS4/ IS1
AUTOGEN™ X4	G168*	G179	DF4/ IS4/ IS1
DYNAGEN™ X4	G156	G156	DF1/ IS4/ IS1
DYNAGEN™ X4	G158	G158	DF4/ IS4/ IS1
INOGEN™ X4	G146	G146	DF1/ IS4/ IS1
INOGEN™ X4	G148	G148	DF4/ IS4/ IS1
ORIGEN™ X4	G056	G056	DF1/ IS4/ IS1
ORIGEN™ X4	G058	G058	DF4/ IS4/ IS1

*AUTOGEN X4 will be investigational in the US during a portion of the study

4.7.1. PaceSafe Feature Overview

The PaceSafe feature consists of two independent automatic pacing threshold determination algorithms: Right Atrial AutoThreshold (RAAT), and Right Ventricular AutoThreshold (RVAT) in AUTOGEN X4. The PaceSafe feature is designed to dynamically adjust the pacing output, independently in each chamber, to ensure capture by optimizing the output voltage to an adequate safety margin.

The PaceSafe algorithm will be studied in a separate clinical study.

Please refer to the AUTOGEN X4 Physician's Technical Guide for more information regarding PaceSafe.

Note: Although PaceSafe will be investigational in the US during a portion of the NAVIGATE X4 Study, investigators may program the feature ON at their discretion. Programming of these features will be collected for NAVIGATE X4.

4.7.1. RightRate Feature Overview

The international AUTOGEN X4 models (G177, G179) will also include the RightRate feature that uses the minute ventilation sensor as a rate driver for subjects with chronotropic incompetence. The RightRate feature is not available in AUTOGEN X4 models in the US (G166, G168).

Please refer to the AUTOGEN X4 Reference Guide for additional information on the RightRate feature.

5. OBJECTIVES

The objective of the NAVIGATE X4 Clinical Study is to gather data to establish the safety, performance and effectiveness of the ACUITY X4 quadripolar coronary venous leads and the RELIANCE 4-FRONT ventricular defibrillation leads to satisfy FDA requirements for pre-market submission. Additionally, data from this study will be used to support post-market approval requirements for the ACUITY X4 and RELIANCE 4-FRONT leads.

6. ENDPOINTS

6.1. *ACUITY X4 Endpoints*

The following endpoints will be evaluated to establish safety, performance, and effectiveness of the ACUITY X4 leads to satisfy US regulatory requirements.

6.1.1. Safety Endpoints

- Primary Safety Endpoint: Lead-related CFR from Implant through 6 Months Post-Implant.
- Ancillary Safety Objective: Chronic Lead-related CFR through 60 Months Post-Implant (Data from the NAVIGATE X4 Clinical Study will be pooled with data from a separate Post-Market Approval Study for analysis of this objective)

6.1.2. Effectiveness Endpoints

- Primary Effectiveness Endpoint 1: LV Lead Pacing Capture Thresholds in the programmed configuration at 3 months post-implant for ACUITY X4 [redacted] Responders are defined as subjects with PCT ≤ 2.5 V in the programmed configuration
- Primary Effectiveness Endpoint 2: LV Lead Pacing Capture Thresholds in the proximal zone (E2, E3, or E4) at 3 months post-implant for ACUITY X4 [redacted]
- Secondary Effectiveness Endpoint 1: Sensed Amplitude in the programmed configuration at Three Months Post-Implant
- Secondary Effectiveness Endpoint 2: Pacing Impedance in the programmed configuration at Three Months Post-Implant

6.2. *RELIANCE 4-FRONT Endpoints*

The following endpoints will be evaluated to establish safety, performance, and effectiveness of the RELIANCE 4-FRONT leads, to satisfy US regulatory requirements.

6.2.1. Safety Endpoints

- Primary Safety Endpoint 1: Lead-related CFR from Implant through 3 Months Post-Implant
- Primary Safety Endpoint 2: Lead-related CFR from 3 through 24 Months Post-Implant
- Secondary Safety Endpoint: Detection of VT/VF within 30 days of implant
- Ancillary Safety Objective: Chronic Lead-related CFR through 60 Months Post-Implant (Data from the NAVIGATE X4 Clinical Study will be pooled with data from a separate Post-Market Approval Study for analysis of this objective)

6.2.2. Effectiveness Endpoints

- Primary Effectiveness Endpoint: RV Lead Pacing Capture Threshold at 0.5 ms pulse width at Three Months Post-Implant
- Secondary Effectiveness Endpoint 1: Sensed Amplitude at Three Months Post-Implant
- Secondary Effectiveness Endpoint 2: Pacing Impedance at Three Months Post-Implant
- Secondary Effectiveness Endpoint 3: VT/ VF Shock Conversion, analyzed within 30 days of implant

7. DESIGN

The NAVIGATE X4 Clinical Study is a prospective, single-arm, non-randomized, multi-center, global clinical study, utilizing performance goals, to demonstrate the safety, performance and effectiveness of the ACUITY X4 LV and RELIANCE 4-FRONT RV Leads. [redacted]

7.1. *Scale and Duration*

The NAVIGATE X4 Clinical Study will [redacted] to enroll between 1542 and 2290 subjects at up to 125 centers in the United States, Israel, and Canada. [redacted] ACUITY X4 leads are required to be implanted or attempted, whereas RELIANCE 4-FRONT is [redacted]

Subjects will be consented and followed for 5 years following implant to fulfill worldwide regulatory post-market approval requirements. See Figure 3.

Figure 3: NAVIGATE X4 Clinical Study Design

7.2. *Justification for the Study Design*

To appropriately characterize performance of new lead families, the United States Food and Drug Administration (FDA) requires that the various leads in a lead family be studied with minimum sample sizes for each depending on the type of lead.

restrictions.

[redacted]

8. SUBJECT SELECTION

8.1. *Study Population and Eligibility*

Subjects included in the NAVIGATE X4 Clinical Study should be selected from the investigator's general patient population indicated for CRT-D implantation. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study as described in Sections 8.2 and 8.3 below.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical study, provided no exclusion criterion (see Section 8.3) is met.

- Subjects indicated for a CRT-D that fulfill one of the following 5 criteria[1]:
  1. Subject with LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and a NYHA class II, III or ambulatory IV symptoms on GDMT*
  2. Subject with LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT*
  3. Subject with LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ ambulatory class IV symptoms on GDMT*
  4. Subject with atrial fibrillation and LVEF less than or equal to 35% on GDMT* if a) the subject requires ventricular pacing or otherwise meets CRT criteria [listed here] and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT
  5. Subject on GDMT* who have LVEF less than or equal to 35% and are undergoing new device placement with anticipated requirement for significant (>40%) ventricular pacing

     *GDMT = Guideline-directed medical therapy (formerly known as optimal pharmaceutical therapy (OPT)), represents optimal medical therapy as defined by ACCF/ AHA guideline-recommended therapies (primarily Class I)
- Subject is intended to receive the ACUITY X4 LV lead and RELIANCE 4-FRONT RV lead (optional in Study Phase 1) and BSC CRT-D with quad header as their initial (*de novo*) cardiac implants
- Subject is willing and capable of providing informed consent (which can include the use of a legally authorized representative (LAR) for documentation of informed consent) and participating in all testing associated with this investigation at an approved center and at the intervals defined by this protocol

- Subject is age 18 or above, or of legal age to give informed consent specific to state and national law

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical study.

- Subject has a known or suspected sensitivity to dexamethasone acetate (DXA)
- Subject has a mechanical tricuspid heart valve
- Subject is enrolled in any other concurrent study, with the exception of local mandatory governmental registries and observational studies/registries* that are not in conflict and do not affect the following:
    - Schedule of procedures for the Study (i.e. should not cause additional or missed visits);
    - Study outcome (i.e. involve medications that could affect the heart rate of the subject);
    - Conduct of the Study per GCP/ ISO 14155:2011/ 21 CFR 812, local regulations
- Subject is currently on the active heart transplant list
- Subject has a documented life expectancy of less than twelve months
- Women of childbearing potential who are or might be pregnant at the time of study enrollment or CRT-D System implant (method of assessment upon physician's discretion)
- Subjects currently requiring chronic dialysis

*Sponsors of such studies/registries should be informed and Boston Scientific must be informed by the investigator about the parallel conduct of these projects in the subject and of the project's basic nature. The decision if a desired mandatory governmental registry or observational study/ registry is in conflict with this exclusion criterion is up to the enrolling investigator.

9. SUBJECT ACCOUNTABILITY

9.1. *Point of Enrollment*

Subjects will be considered enrolled into the NAVIGATE X4 Clinical Study at the time of informed consent form execution. All subject enrollments will be counted against the enrollment ceiling for the study.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems

related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal may include physician discretion, subject choice to retire consent, loss to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable electronic case report form (eCRFs) up to the point of subject withdrawal and an "End of Study" eCRF must be completed. For subjects who are "lost-to-follow-up" the investigator/ center should have at least three documented attempts to contact the subject prior to completion of the "End of Study" eCRF. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used.

9.3. *Subject Status and Classification*

All patients who sign the Informed Consent form are considered enrolled in the study and count towards the enrollment ceiling. Subjects will be classified in the study database as follows:

Intent - refers to a subject who has been enrolled, but then does not undergo an implant procedure. The original Informed Consent form and screening documentation for intent patients should be maintained in the Center's files. There are no follow-up requirements for intent subjects; intent subjects must be withdrawn from the study.

Partial Attempt – refers to a subject who has been enrolled and has had anesthesia administered in preparation for the surgical implant procedure, but does not have an ACUITY X4 or RELIANCE 4-FRONT lead introduced into their vasculature. There are no follow-up requirements for partial attempt subjects; partial attempt subjects must be withdrawn from the study.

Note: In this case since neither study lead was implanted, US subjects may not be implanted with an AUTOGEN X4 CRT-D (while it is investigational)

Attempt - refers to a subject who 1) has been enrolled in the NAVIGATE X4 Study, 2) has had anesthesia administered in preparation for the surgical implant procedure, 3) has had either the ACUITY X4 or RELIANCE 4-FRONT lead introduced into the subject's vasculature, but 4) is not successfully implanted with either the ACUITY X4 lead or RELIANCE 4-FRONT lead.

Note: In this case since neither the RELIANCE 4-FRONT lead nor the ACUITY X4 lead was implanted, US subjects may not be implanted with an AUTOGEN X4 CRT-D (while it is investigational)

Attempt subjects must be followed 30 ± 7 days post-attempted ACUITY X4 and/or RELIANCE 4-FRONT lead implant to assure there are no associated adverse events, or to assure the resolution of any adverse events associated with the attempted ACUITY X4 and/ or RELIANCE 4-FRONT lead implants. These subjects must be withdrawn from the study after satisfying the 30 ± 7 day follow up.

Implant - refers to a subject who is successfully implanted and/or tested with the ACUITY X4 and/or RELIANCE 4-FRONT Lead(s) per the study protocol. These subjects are

followed in accordance with the follow-up schedule included in this protocol and included in all analyses of safety, effectiveness, and performance.

9.4. *Enrollment Controls*

To support regulatory requirements approximately 1840 subjects [redacted] will be enrolled per this protocol. Investigational sites will be notified when the enrollment goal for each cohort is close to being reached and once enrollment for each cohort is complete. See Section 7.2 for more information on the study cohorts.

9.5. *End-of-Study Action Plan*

Boston Scientific Corporation reserves the right to terminate the study, or discontinue implanting one of the two study leads at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. In the event of this occurrence, BSC will communicate to the investigators of the NAVIGATE X4 Clinical Study. The investigators will be responsible for communicating any information necessary to the subjects. BSC will support the physicians by providing recommendations for ensuring the safety of the subjects and the handling of the investigational devices (AUTOGEN X4 CRT-D, ACUITY X4 leads, and/or RELIANCE 4-FRONT leads) which may include, but are not limited to:

- Standard of care procedures
- More frequent follow ups of the subject and the lead(s) than per standard procedures
- Longer term follow up (beyond consented 5-year period)
- Explantation of ACUITY X4 and/ or RELIANCE 4-FRONT leads
- Explantation of AUTOGEN X4 CRT-D
- Other possible actions

10. STUDY METHODS

10.1. *Data Collection*

The data collection schedule for this study is shown in Table 7 below. A reminder that the NAVIGATE X4 Clinical Study is [redacted] ACUITY X4 is required to be implanted or attempted [redacted] and RELIANCE 4-FRONT is [redacted] required to be implanted or attempted [redacted]

Table 7: Data Collection Schedule for NAVIGATE X4 Clinical Study

Procedure/ Assessment	Enroll-ment	Implant	Pre-Discharge	3 Months	6 Months	Semi-annual Visits through 5 Years	Add'l Visits
Timeframe	≤ 30 d prior to Implant	Implant	3-72 h* Clinic Visit	91±21 d* Clinic Visit	182±21 d* Clinic Visit	12 Mo: 365±45 d* 18 Mo: 547±45 d* 24 Mo: 730±45 d* 2 ½ Yr: 913±45 d* 3 Yr: 1095±45 d* 3 ½ Yr: 1278±45 d* 4 Yr: 1461±45 d* 4 ½ Yr: 1643±45 d* 5 Yr: 1826±45 d* Clinic Visit	Not specified
ICF Process	**X**	--	--	--	--	--	--
Subject demographics	**X**	--	--	--	--	--	--
Physical assessment	**X**	--	--	--	--	--	--
Medical history	**X**	--	--	--	--	--	--
PSA measurements for all leads (pacing threshold(s) @ 0.5ms)	--	**X (X4 leads, [redacted] else O**	--	--	--	--	--
PA and lateral CXR and/or fluoro image of X4 and 4-FRONT lead distal tip fixation	--	**X (Either/ or, not both)**		--	--	--	--
Ventricular tachyarrhythmia induction	--	**O**		--	--	--	--
Shock Therapy for Spontaneous Ventricular Arrhythmias	--	**X**	**X**	**X**	**X**	**X**	**O**
Class I/ III Antiarrhythmic Medications including updates and changes	**X**	**X**	**X****	**X****	**X****	**X****	**O****
Documentation of PaceSafe Programming	--	**X**	**X**	**X**	**X**	**X**	**O**
PG lead measurements (sensed amplitude, impedance, shock lead impedance and PCT) for all implanted leads (pacing threshold(s) for RV and LV @ 0.5ms through 3 Month follow up)	--	**X**	**X**	**X**	**X**	**X**	**X** (if lead-related AE), else **O**
ECG from PRM documenting LOC	--	**X**	**X**	**X**	--	--	**O**
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Protocol Deviations	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Legend: X = Required; **- -** = Not required/ Not applicable; **O** = Optional;

*Clock Starts after end of implant procedure, day of implant is day 0 and hour 0 is pocket closure

**Collection of Class I/III antiarrhythmic medications for lead-related adverse events

h = hours; **d** = days; **yr** = year; **AE** = Adverse Event; **ECG** = Electrocardiogram; **LOC** = Loss of Capture; **PG** = Pulse Generator; **PSA** = Pacing System Analyzer

10.2. *Study Candidate Screening*

Boston Scientific will collect information to document potential subjects who are considered as NAVIGATE X4 Study candidates but are determined not to meet inclusion criteria prior to signing informed consent.

10.3. *Informed Consent*

Subjects who meet all of the inclusion criteria and none of the exclusion criteria and agree to participate in the NAVIGATE X4 Clinical Study must give written informed consent approved by the regional regulatory body and the investigational center's Institutional Review Board (IRB) or Ethics Committee (EC) prior to study participation and use of any investigational leads or testing/ data collection. The Informed Consent Form (ICF) must be in a language understandable to the subject and if needed, Boston Scientific will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Subjects will be considered enrolled into the NAVIGATE X4 Clinical Study at the time the subject signs and dates the ICF.

10.4. *Enrollment Visit*

The data to be collected during enrollment into the NAVIGATE X4 Clinical Study includes patient demographic data, a physical assessment of the subject, including height and weight, vital signs, arrhythmia history, cardiac disease history, indications, and current cardiovascular medications. No study-specific procedures, device implant, or data collection may be conducted prior to consent.

Implant or attempted implant of the ACUITY X4 and/ or RELIANCE 4-FRONT Lead(s) must occur within 30 days of the subject signing informed consent.

10.4.1. Source Documentation Requirements

See Table 10 for required source documentation of the enrollment visit.

10.5. *Implant Visit*

The PG, investigational leads (ACUITY X4 and/ or RELIANCE 4-FRONT), and any other commercially available leads should be implanted and tested per standard procedures and in accordance with the Physician's Manuals for the associated PG and leads.

10.5.1. Pulse Generator Selection

Only a commercially available Boston Scientific Cardiac Resynchronization Therapy Defibrillator (CRT-D) with a quad header, or AUTOGEN X4 CRT-D (investigational in the US, see Section 4.7 for more detail) may be used in the NAVIGATE X4 Clinical Study*.

*__Note__: in the event ACUITY X4 is attempted but not successfully implanted, BSC PGs (including ICDs) are allowed.

10.5.2. Atrial Lead Selection

Any commercially available atrial pace/sense lead may be used. Boston Scientific leads are preferred and recommended.

10.5.3. Right Ventricular Lead Selection

10.5.3.1. [redacted] NAVIGATE X4

Any commercially available Boston Scientific cardioversion/defibrillation lead may be used [redacted] NAVIGATE X4. BSC recommends the use of RELIANCE 4-FRONT. Documentation of RV lead choice will be collected [redacted] NAVIGATE X4.

10.5.3.2. [redacted] NAVIGATE X4

RELIANCE 4-FRONT is required in [redacted] NAVIGATE X4. If RELIANCE 4-FRONT is attempted, but not successfully implanted, the subject may still be a part of the study [redacted] and a commercially available RV lead is acceptable. Boston Scientific RV leads are required.

10.5.3.3. RELIANCE 4-FRONT

When implanting RELIANCE 4-FRONT Active Fixation Leads, view the radiopaque markers under fluoroscopy to identify when the fixation helix is fully extended. Full extension is achieved when the radiopaque markers are joined and the fixation helix is extended outside the distal fluoroscopy markers (the expected number of rotations is 11 turns for 59 and 64 cm and 12 turns for 70 cm). Refer to Figure 4.

Figure 4: Fluoroscopic Views of the RELIANCE 4-FRONT Active Fixation Lead Helix

10.5.4. LV Lead Selection

Subjects enrolled in the NAVIGATE X4 study are required to be implanted and/ or attempted with an ACUITY X4 lead. In the event an ACUITY X4 lead is attempted, but not successfully implanted, only a market-released BSC unipolar or bipolar coronary venous lead is acceptable.

Note: In the event a BSC LV lead other than ACUITY X4 is implanted, data collected on these leads must follow that of sections 10.5.8, 10.5.11, 10.6.2, 10.7.2, and 10.8.1 (for RA and RV leads).

10.5.5. ACUITY X4 Left Ventricular Lead Selection

When selecting the appropriate ACUITY X4 lead for a subject, use the following guidelines.

Use venogram to identify a suitable target vein for lead implantation.
The three ACUITY X4 lead tip configurations (Spiral S, Spiral L, and Straight) are available to provide appropriate choice for a variety of coronary veins. See below and Figure 5.

- ACUITY X4 Spiral L is recommended when a target vein reaches the apical-third region of the heart, or mid-third of a severely dilated heart
- ACUITY X4 Spiral S is recommended when a target vein reaches only the mid-third of the heart
- ACUITY X4 Straight is recommended when a target vein is short, narrow, or torturous

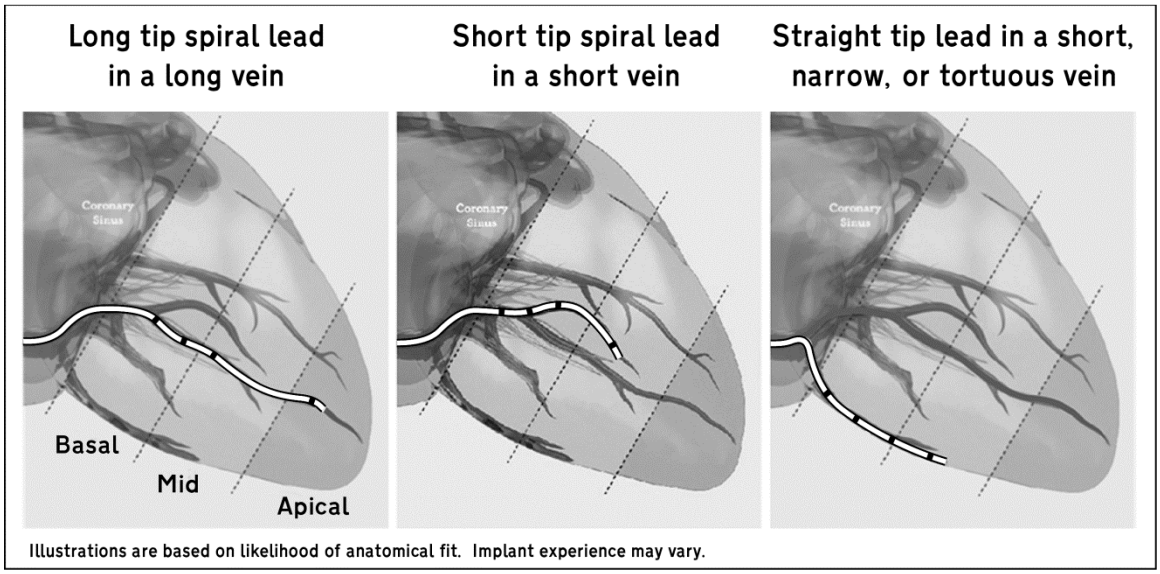


Figure 5: ACUITY X4 Lead Selection

10.5.6. LV Lead Delivery Method Selection

The choice of the LV lead delivery system is left to physician discretion. Data regarding LV lead delivery method will be collected as a part of the NAVIGATE X4 Study database. Boston Scientific LV lead delivery systems are preferred and recommended.

10.5.7. Baseline ACUITY X4 Lead Measurements with PSA [redacted]

Documentation of PSA measurements for ACUITY X4 leads will be required as described below for NAVIGATE X4 Study [redacted]. [redacted]

The required data to be collected from the implant procedure for all ACUITY X4 includes PCT at 0.5 ms pulse width, sensed amplitude, and pacing impedance, measured with a pacing system analyzer (PSA) to verify adequate signals. Refer to Figure 6 below for a picture of the relationship between the terminal pin and ring contacts on the ACUITY X4 quadripolar lead.

As stated in the ACUITY X4 Physician's Lead manual as a warning, only use the ACUITY X4 Connector Tool for electrical connections to PSAs or similar monitors. Do not attach alligator

clips directly to the lead terminal or damage could occur. During [redacted] NAVIGATE X4, it is required to perform a minimum of 6 threshold measurements as summarized in Table 8 and Figure 7 below. First, test 4 extended bipolar or 4 unipolar configurations (per physician discretion) to determine adequate electrode-myocardium contact. Test for the presence of extracardiac or phrenic nerve stimulation (PNS) for each electrode by pacing the lead at a high voltage output, using professional medical judgment to select the output voltage. If extracardiac stimulation is detected, measure stimulation PNS threshold. The four extended bipolar, or unipolar, measurements provide a relative threshold ranking among the electrodes which is associated to the proximity of each electrode to viable myocardium. Although thresholds may change, the relative ranking will be the same for bipolar measurements. Then select 2 bipolar measurements (one pair from E1 as the cathode (E2, E3, or E4 as the anode) and the other pair from E2, E3 or E4 as the cathode) to confirm the preferred distal and proximal pacing options. Use the best extended bipolar or unipolar ring electrode (from E2, E3, E4) as a cathode to any other ring electrode as an anode. Again, test for the presence of extracardiac or phrenic nerve stimulation for each electrode. If stimulation is detected, measure a PNS threshold. Refer to Table 8, Figure 6 and Figure 7 below.

The final test results of this testing must be printed from the PSA or documented on the Implant technical source documentation form and must be recorded on the Implant eCRF. BSC will also collect the PSA manufacturer and model number. Use the following figure to assist in connecting the ACUITY X4 lead to the PSA using the ACUITY X4 connector tool.

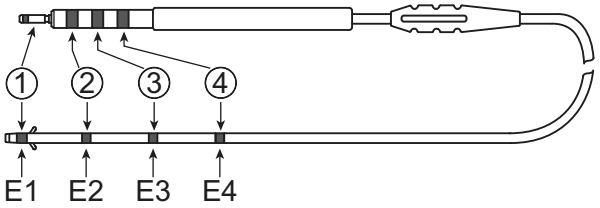


Figure 6: Relationship between the terminal pin and ring contacts with the distal tip electrodes E1 – E4

Table 8: ACUITY X4 PSA Testing Required during Implant

Pacing Configurations	# of Configurations and PNS Testing
Unipolar or extended bipolar measurements from each electrode, E1 through E4	**4**
Bipolar measurements between 2 of the electrodes: E1 →E2 E1 →E3 E1 →E4	**2**
Total configurations tested with PSA	**6**

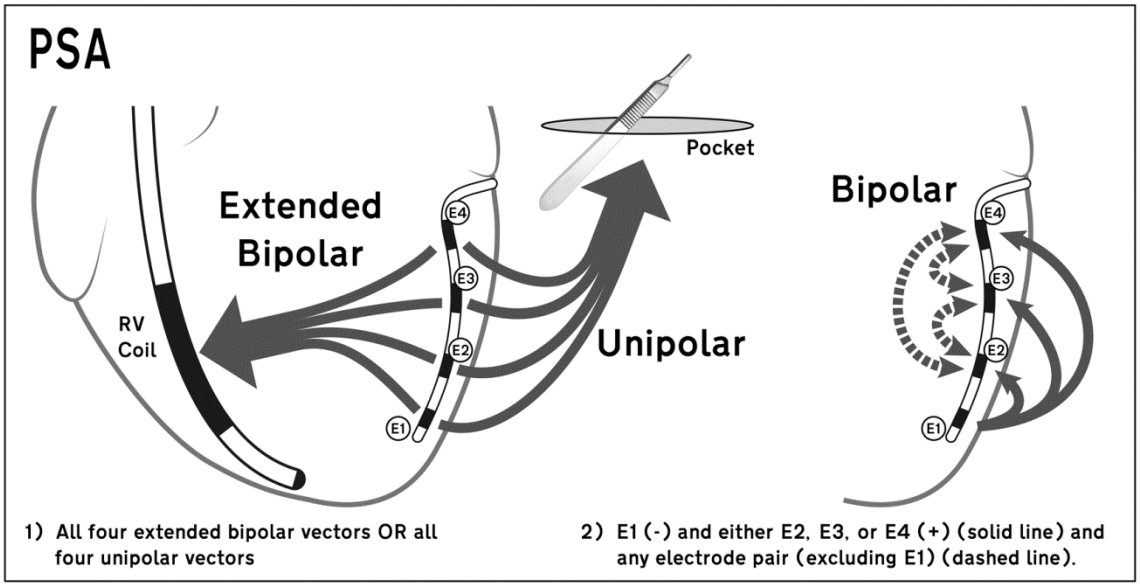


Figure 7: ACUITY X4 Configurations to be Tested with PSA

10.5.8. Baseline PSA Measurements for RA and RV Leads [redacted]

The optional data to be collected from the implant procedure for RA and RV leads, as well as ACUITY X4 [redacted] includes pacing threshold, sensed amplitude, and pacing impedance, measured with a PSA to verify adequate signals before attaching the lead to the PG.

10.5.9. Loss of Capture and Threshold Definition

During the NAVIGATE X4 Study PCT measurements from the PG are collected from leads implanted in the LV, RA and RV in the standard manual fashion. At least 3 cardiac cycles at a given voltage level shall be obtained before stepping down to the next voltage level. A count of two non-capture beats is required at a given voltage level to declare a loss of capture (LOC) for any of these tests. The threshold is defined as one voltage level above the level where two non-captured beats are observed.

10.5.10. ACUITY X4 Lead Measurements with PG

Lead measurements, including pacing threshold (at 0.5 ms pulse width), sensed amplitude, and pacing impedance, are required to be collected using the CRT-D at implant for all implanted ACUITY X4 Leads. Pacing and sensing evaluation using the PG must be performed and the results recorded on the Implant eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all ACUITY X4 Leads:

- Intrinsic amplitude (mV)*
- Pacing threshold (V, at 0.5 ms pulse width), details below in Table 9 and Figure 8
- Pacing lead impedance (Ω)*

*Note: the configuration used for sensed amplitude and lead impedance measurements is upon physician discretion. The nominal sensing configuration for ACUITY X4 is E1 →E2 (LV Tip 1 →LV Ring 2).

The pacing configurations that require PCT testing at the implant (through three-month follow up) are listed in Table 9 below and shown in Figure 8. If the investigator chooses to conduct multiple pacing threshold tests or on configurations not listed below on the ACUITY X4 Lead, only the final measurement and none of the initial measurements taken at 0.5 ms pulse width must be indicated on the eCRF.

Table 9: ACUITY X4 Pacing Configuration Required for PCT Testing at Implant, Pre-D and Three Months Post Implant

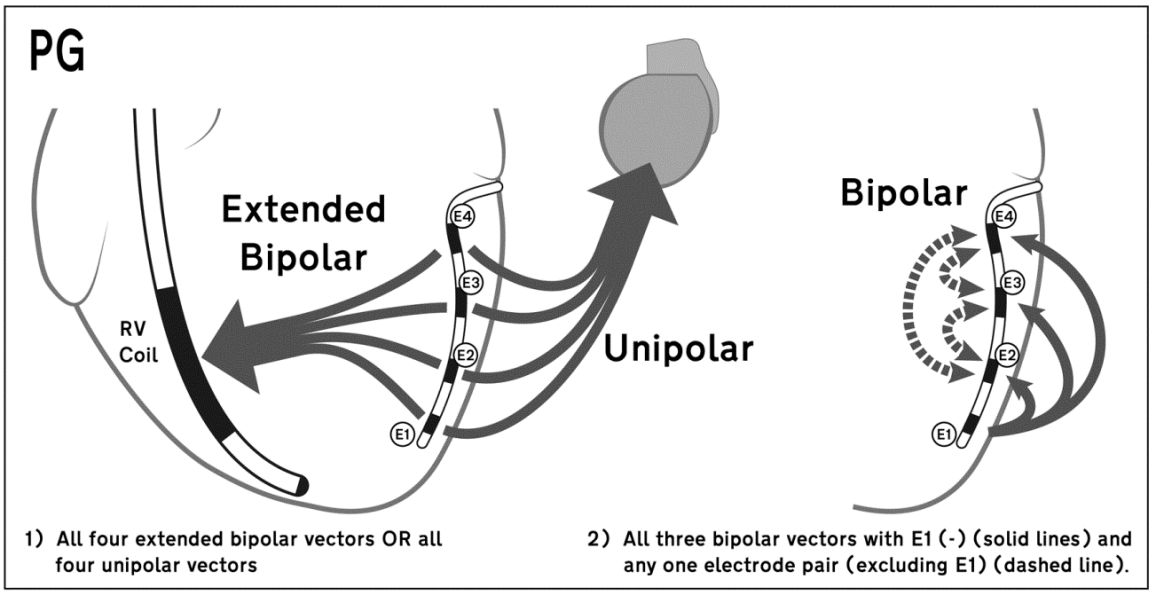
Pacing Configurations	# of Configurations tested
Unipolar or extended bipolar measurements from each electrode, E1 through E4	**4**
Bipolar between electrodes$^{\Delta}$: E1 →E2 E1 →E3 E1 →E4	**3**
Bipolar from the best electrode* on the lead to another electrode on the lead (excluding E1)	**1**
Total configurations tested	**8**

* Best electrode is the one that has the lowest threshold without phrenic nerve stimulation (PNS). In the event of a "tie" for best electrode, the investigator should use their medical judgment to select the best.

$^{\Delta}$ Nomenclature of electrodes on the lead (E1, E2, E3, E4) is an industry standard. The corresponding nomenclature on the BSC PRM is as follows:

- E1: LV Tip 1
- E2: LV Ring 2
- E3: LV Ring 3
- E4: LV Ring 4

Figure 8 below depicts the measurements required for the ACUITY X4 leads as described in the table above.



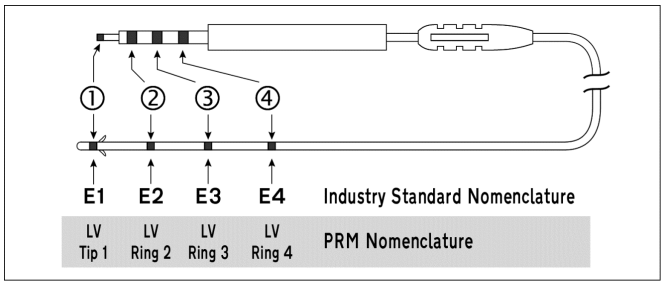


Figure 8: ACUITY X4 Lead Measurements Required at Implant, Pre-D and 3 Months

10.5.10.1. Phrenic Nerve Stimulation (PNS) Testing

Test for PNS in all aforementioned configurations and measure the PNS threshold if detected in the programmed configuration. The PNS threshold must be documented on the Implant technical source documentation form and must be recorded on the Implant eCRF.

10.5.11. RA and RV Lead Measurements with PG

Lead measurements, including pacing threshold, sensed amplitude, pacing impedance, and shock impedance are required at implant for all implanted RA (regardless of model) and RV Leads (RELIANCE 4-FRONT or commercially available RV lead). Pacing and sensing evaluation using the PG must be performed and the results recorded on the Implant eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm or is in atrial fibrillation). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all RA and RV Leads:

- Intrinsic amplitude (mV)
- Pacing threshold (V, at 0.5 ms pulse width; pulse width requirement for RELIANCE 4-FRONT leads only)

- Pacing impedance and
- Shock lead impedance (Ω)

If the investigator chooses to conduct multiple pacing threshold tests on the RA and/or RV Lead, only the final measurement and none of the initial measurements must be indicated on the eCRF.

10.5.12. Optional Ventricular Tachyarrhythmia Induction

Subjects are not required to undergo induction testing. Those subjects that undergo induction testing within 30 days of implant, per the discretion of the investigator, will be included in the analysis of the 4-FRONT Secondary Safety Endpoint and the 4-FRONT Secondary Effectiveness Endpoint 3. See Sections 11.2.4 and 11.2.8, respectively, for more information on these endpoints. The method of induction is per the physician's discretion but BSC strongly recommends the programmer/ PRM electrogram be run continuously during induction and delivery of therapy. VT/VF will be induced and the device allowed to sense and detect the arrhythmia (VT/VF Detection Time) and deliver programmed therapy (VT/VF Shock Conversion). The investigator shall allow the device to deliver at least one shock prior to external rescue, if appropriate. If multiple shock lead configurations (different shock vectors, polarities or lead positions) are tested, data from the final configuration must be used to document both detection time and shock conversion. VT/VF Detection Time is defined as the interval starting 250 ms after the last induction artifact (the time of the post induction ventricular refractory period) and ending at the "V-Episode Declared" marker. Programming of detection and duration should remain at nominal settings .

Steps for VT/VF induction:

1. Run programmer/PRM paper
2. Induce VT/VF
3. Allow device to sense and detect arrhythmia. Measure and record detection time.
4. Allow device to deliver therapy. Record conversion efficacy from final configuration.

If not done at implant, the physician may complete the optional VT/VF induction testing at pre-discharge or within 30 days of implant (at an additional follow up). Subjects may have additional VT/VF testing done if deemed appropriate.

10.5.13. Source Documentation Requirements

See Table 10 for required source documentation of the implant procedure.

10.6. *Pre-Discharge Visit*

The pre-discharge follow-up visit must be performed between 3 hours and 72 hours after implant. If the subject needs to stay more than 72 hours in the hospital after implant for any reason, the pre-discharge procedure should still be performed within 72 hours of implant. Any reasons for a prolonged or ongoing hospitalization need to be appropriately documented (i.e. Adverse Event Form, if applicable).

10.6.1. ACUITY X4 Lead Measurements with PG

Lead measurements, including pacing threshold (at 0.5 ms pulse width), sensed amplitude, and pacing impedance, are required to be collected at the pre-discharge visit for all implanted ACUITY X4 Leads. Pacing and sensing evaluation using the PG must be performed and the results recorded on the Pre-Discharge eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all ACUITY X4 Leads:

- Intrinsic amplitude (mV)*
- Pacing threshold (V, at 0.5 ms pulse width), details below in Table 9 and Figure 8
- Pacing lead impedance (Ω)*

*Note: the configuration used for sensed amplitude and lead impedance measurements is upon physician discretion. The nominal sensing configuration for ACUITY X4 is E1 →E2 (LV Tip 1 →LV Ring 2).

If the investigator chooses to conduct multiple pacing threshold tests or on configurations not listed below, on the ACUITY X4 Lead, only the final measurement and none of the initial measurements taken at 0.5 ms pulse width must be indicated on the eCRF. The pacing configurations that require testing at the Pre-Discharge visit are listed in Table 9 and Figure 8.

10.6.1.1. PNS Testing

Test for PNS in all aforementioned configurations and measure the PNS threshold if detected in the programmed configuration. The PNS threshold must be documented on the Pre-Discharge technical source documentation form and must be recorded on the Pre-Discharge eCRF.

10.6.2. RA and RV Lead Measurements with PG

Lead measurements, including pacing threshold, sensed amplitude, pacing impedance, and shock impedance are required at the pre-discharge visit for all implanted RA (regardless of model) and RV Leads (RELIANCE 4-FRONT or commercially available RV lead). Pacing and sensing evaluation using the PG must be performed and the results recorded on the Pre-Discharge Visit eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm or is in atrial fibrillation). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all RA and RV Leads:

- Intrinsic amplitude (mV)
- Pacing threshold (V, at 0.5 ms pulse width; pulse width requirement for RELIANCE 4-FRONT RV leads only)
- Pacing impedance and
- Shock lead impedance (Ω)

If the investigator chooses to conduct multiple pacing threshold tests on the RA and/or RV Lead, only the final measurement and none of the initial measurements must be indicated on the eCRF.

10.6.3. Optional Ventricular Tachyarrhythmia Induction

If not done at implant, the physician may complete the optional VT/VF induction testing at Pre-Discharge or within 30 days of implant (at an additional follow up), as described in Section 10.5.12. Subjects may have additional VT/VF testing done if deemed appropriate.

10.6.4. Shock Therapy for Spontaneous Ventricular Tachyarrhythmia

Record the following information for any spontaneous ventricular tachyarrhythmia that is treated with shock therapy: episode number, episode date, episode attempt number, episode type, therapy delivered, energy delivered, device classification, investigator classification, and return to normal sinus rhythm.

10.6.5. Source Documentation Requirements

See Table 10 for required source documentation for the Pre-Discharge visit.

10.7. *Three-Month Visit*

The three-month visit must be performed as a clinic visit at 91 ± 21 days after implant.

10.7.1. ACUITY X4 Lead Measurements with PG

Lead measurements, including pacing threshold (at 0.5 ms pulse width), sensed amplitude, and pacing impedance, are required to be collected at the three-month visit for all implanted ACUITY X4 Leads. Pacing and sensing evaluation using the PG must be performed and the results recorded on the three-month visit eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all ACUITY X4 Leads:

- Intrinsic amplitude (mV)*
- Pacing threshold (V, at 0.5 ms pulse width), details below in Table 9 and Figure 8
- Pacing lead impedance (Ω)*

*Note: the configuration used for sensed amplitude and lead impedance measurements is upon physician discretion. The nominal sensing configuration for ACUITY X4 is E1 →E2 (LV Tip 1 →LV Ring 2).

If the investigator chooses to conduct multiple pacing threshold tests or on configurations not listed below, on the ACUITY X4 Lead, only the final measurement and none of the initial measurements taken at 0.5 ms pulse width must be indicated on the eCRF. The pacing configurations that require testing at the three-month visit are listed in Table 9 and Figure 8 in Section 10.5.10.

10.7.1.1. PNS Testing

Test for PNS in all aforementioned configurations and measure the PNS threshold if detected in the programmed configuration. The PNS threshold must be documented on the Three-Month technical source documentation form and must be recorded on the Three-Month eCRF.

10.7.2. RA and RV Lead Measurements with PG

Lead measurements, including pacing threshold, sensed amplitude, pacing impedance, and shock impedance are required at the three-month visit for all implanted RA (regardless of model) and RV Leads (RELIANCE 4-FRONT or commercially available RV lead). Pacing and sensing evaluation using the PG must be performed and the results recorded on the three-month visit eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm or is in atrial fibrillation). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all RA and RV Leads:

- Intrinsic amplitude (mV)
- Pacing threshold (V, at 0.5 ms pulse width; pulse width requirement for RELIANCE 4-FRONT RV leads only)
- Pacing impedance and
- Shock lead impedance (Ω)

If the investigator chooses to conduct multiple pacing threshold tests on the RA and/or RV Lead, only the final measurement and none of the initial measurements must be indicated on the eCRF.

10.7.3. Shock Therapy for Spontaneous Ventricular Tachyarrhythmia

Record the following information for any spontaneous ventricular tachyarrhythmia that is treated with shock therapy: episode number, episode date, episode type, therapy delivered, device classification, investigator classification, return to normal sinus rhythm.

10.7.4. Source Documentation Requirements

See Table 10 for required source documentation for the three-month visit.

10.8. *Semi-Annual Clinic Visits from 6 months through 5 years (6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months)*

Semi-annual visits are required to be conducted as clinic visits for NAVIGATE X4 subjects, starting at six months post implant and continuing until 5 years post implant. Specifically, timing for each follow up is based on the subject's implant date:

- 6 Month Follow-up: 182 ± 21 days
- 12 Month Follow-up: 365 ± 45 days
- 18 Month Follow-up: 547 ± 45 days
- 24 Month Follow-up: 730 ± 45 days
- 30 Month Follow-up: 913 ± 45 days
- 36 Month Follow-up: 1095 ± 45 days

- 42 Month Follow up: 1278 ± 45 days
- 48 Month Follow-up: 1461 ± 45 days
- 54 Month Follow-up: 1643 ± 45 days
- 60 Month Follow-up: 1826 ± 45 days

10.8.1. ACUITY X4, RA and RV Lead Measurements with PG

Lead measurements, including pacing threshold, sensed amplitude, pacing impedance, and shock impedance are required to be collected for all implanted LV, RA and RV leads at each semi-annual visit, starting at the six-month visit, through 5 years post-implant. Pacing and sensing evaluation using the PG must be performed and the results recorded on the appropriate semi-annual visit eCRF. Lead measurements are required unless the testing is prohibited by a subject's condition (subject has no intrinsic rhythm or is in atrial fibrillation). The following measurements are to be taken utilizing the PG to ensure adequate sensing and pacing function of all implanted LV, RA and RV leads:

- Intrinsic amplitude (mV)
- Pacing threshold (V, pulse width at physician discretion)
- Pacing impedance (Ω) and
- Shock lead impedance (Ω)

If the investigator chooses to conduct multiple pacing threshold tests on the implanted LV, RA or RV leads, only the final measurement and none of the initial measurements must be recorded on the eCRF.

10.8.2. Shock Therapy for Spontaneous Ventricular Tachyarrhythmia

Record the following information for any spontaneous ventricular tachyarrhythmia that is treated with shock therapy: episode number, episode date, episode type, therapy delivered, device classification, investigator classification, return to normal sinus rhythm.

10.8.3. Source Documentation Requirements

See Table 10 for required source documentation for all semiannual follow-ups.

10.9. *Additional Visits*

All follow-ups outside of the designated follow-up windows or multiple visits inside any one follow-up window need to be reported as an additional follow-up if a lead-related adverse event (as defined in Section 19.3) occurred, or the device was interrogated and there was a resulting programming change. If possible, a device evaluation and lead measurements should be performed and the results recorded on the Additional Follow-up eCRF.

In the event of a lead-related adverse event, a device evaluation and lead measurements are required and the results must be recorded on the Additional Follow-up eCRF.

10.9.1. Source Documentation Requirements

See Table 10 for required source documentation for additional follow-ups.

10.10. *LATITUDE Remote Follow-up*

Subjects may be followed on the LATITUDE system (which may include weight scale and blood pressure sensors) from the time they are implanted, if commercially available. However, required NAVIGATE X4 Clinical Study follow ups cannot be substituted with a LATITUDE remote follow up.

10.11. *Source Documents from All Study-Required Visits*

Table 10 below summarizes the source data requirements for this clinical study. Original source documents are required to be retained at the center. On the rare occasion where the original is not available, copies of the original source document must be signed and dated by a member of the investigational center team with a statement that it is a true reproduction of the original source document.

Table 10: Source Documentation Requirements

Requirement	Visit	Disposition
Informed consent documentation process	Enrollment	Retain at Center
Assessment of pregnancy for women of child bearing potential: method of assessment per physician discretion	Enrollment	Retain at Center
Documentation of the following: • Demographics: age at implant, gender • Heart Failure assessment: LVEF, QRS width, GDMT • Vital signs: heart rate, blood pressure • Class I/III Antiarrhythmic medications • Subject's height and weight • Arrhythmia history • Cardiac disease history	Enrollment	Retain at Center
Documentation of the following: • Time of first incision • Time of pocket closure, to document time 0 • Class I/III antiarrhythmic medications that the subject is prescribed *prior to, but not including* the implant procedure • Model and serial number of implanted cardiac devices • Manufacturer and model number of PSA	Implant	Retain at Center
Printout of ACUITY X4 PSA measurements or signed Implant Technical Source Form	Implant	Retain at Center
Printout of PG measurements (sensed amplitude, pacing impedance, shock lead impedance, and pacing capture threshold results) either from PRM printout or a signed Technical Source Form (from applicable visit)	Implant, Follow-ups	Retain at Center
Printout of ECG strip (from PRM) documenting LOC for all implanted leads threshold tests	Implant, Pre-Discharge, 3-Month Follow up	Retain at Center

Table 10: Source Documentation Requirements

PA and lateral chest X-ray or fluoroscopic image of ACUITY X4 and RELIANCE 4-FRONT (as applicable) Lead distal tip fixation	Implant or Pre-Discharge	Retain at Center
Real time programmer/ PRM strip documenting induced VT/VF (if conducted and strip available)	Implant through 30 days post-implant	Retain at Center
Initial Quick Notes report to document programming of PaceSafe features	Implant through 24 Month Follow up	Retain at Center
Class I/III Antiarrhythmic medications	Any applicable visit with a Lead-related Adverse Event	Retain at Center
Documentation of spontaneous shock therapy by saving all to disk (USB drive required); PRM strips are optional: • "Selected Episodes Report" (counters and EGMs required), • "Arrhythmia Logbook", • "Quick Notes" • "Follow up Report"	Any applicable visit	Retain at Center
Adverse events	Any applicable visit	Retain at Center
In the event of subject death: • Death narrative • Relative medical records • Death certificate (if available) • Autopsy report (if available)	Any applicable visit	Submit one copy to Boston Scientific CRV, Retain one copy at center

Abbreviations: **PSA** = Pacing System Analyzer; **PG** = Pulse Generator; **PA** = Posterior-Anterior; **CRF** = Case Report Form; **EGM**= Electrogram

10.12. *Study Completion*

Each subject will complete the study when they have been followed for 5 years after their implant procedure. See Section 12.2 for details on data retention.

10.13. *Exceptions for Use of Investigational Software (associated with the AUTOGEN CRT-D) at Non-Investigational Sites*

While geographic stability is an inclusion criterion at the time of enrollment, it is possible for conditions to change for the subject in which continuing follow-up at the investigational center may pose a challenge. Every attempt should be made to keep the patient at the investigational center and under care of a trained investigator.

In order to protect patient safety, use of investigational software at non-investigational sites may be permitted in exceptional situations with prior sponsor approval. Sponsor approval for use of investigational software will be considered for the following conditions:

- Patient has sought unplanned urgent medical attention at a non-investigational site and software use is intended to protect the health and welfare of the patient

- Health of the patient prevents reasonable safe travel to an investigational site
- Travel to investigational site presents a significant hardship on the patient (e.g. physical distance to an approved investigational site is too great, limited access to transportation to the investigational site, patient is under inpatient care , or patient is seen frequently for recurring treatment, such as dialysis or chemotherapy, at another sites and the investigator agrees to allow device interrogations at that site)

Upon use of the investigational software at a non-investigational site, information is to be collected surrounding the circumstances of use of the investigational software and reported to Boston Scientific CRM within 5 business days.

11. STATISTICAL CONSIDERATIONS

11.1. *ACUITY X4 Endpoints*

11.1.1. ACUITY X4 Primary Safety Endpoints

Safety of the ACUITY X4 lead will be evaluated by the lead-related complication-free rate (CFR) over a six-month follow-up period. [redacted]. Lead-related complications are lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury or death. Lead-related adverse events are further defined in Section 19.3. Lead-related complications associated with attempted ACUITY X4 Lead implants will count toward this safety endpoint.

11.1.1.1. Hypotheses

The following hypotheses will be used to evaluate the Primary Safety Endpoint [redacted]

H_o: The Implant through 6-month lead-related complication-free rate ≤ 87%

H_a: The Implant through 6-month lead-related complication-free rate > 87%

The following hypotheses will be used to evaluate the Primary Safety Endpoint [redacted]

H_o: The Implant through 6-month lead-related complication-free rate ≤ 85%

H_a: The Implant through 6-month lead-related complication-free rate > 85%

[redacted]

[redacted]

11.1.2. Sample Size

The overall sample size required for ACUITY X4 is determined by the Primary Safety Endpoint. Table 12 contains the sample size estimates [redacted] based on the outlined assumptions. The sample size estimates were obtained using the normal approximation to the binomial and verified through simulations based on Kaplan-Meier methodology; Kaplan-Meier methodology will be used for the analyses. [redacted]

11.1.3. Statistical Methods

To assess safety of the ACUITY X4 leads, the Kaplan-Meier six month (180-day) complication-free rate will be calculated. [redacted] The analysis will be conducted when the last 6-month follow-up is completed [redacted] Data from all implanted or attempted [redacted] leads will be included in the endpoint analysis.

[redacted]

The exact follow-up time for each ACUITY X4 lead in the 180-day post-implant period will be included in the analysis via Kaplan-Meier methodology. The leads that fail to reach 180 days of follow-up (without experiencing an endpoint event prior to their end of follow-up in the period) will be censored at the time of their end of follow-up in the period. Because non-informative censoring cannot be assumed for these leads, a tipping point analysis will be performed to determine the potential effects these censored leads could have on the results if full information on each lead was present. The tipping point analysis will assign each lead that was censored prior to 180 days as either having or not having an endpoint event. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis) to failing (null hypothesis rejected). An exact binomial test will be performed for the tipping point analysis.

11.1.4. ACUITY X4 Primary Effectiveness Endpoint 1

The first effectiveness endpoint for ACUITY X4 is pacing capture thresholds (PCT) in the programmed configuration. This endpoint will be evaluated at 3 months post-implant. [redacted] For this endpoint, responders will be defined as subjects with PCT ≤ 2.5 V in the programmed configuration.

11.1.4.1. Hypotheses

The following hypotheses will be used to evaluate Primary Effectiveness Endpoint 1 for X4 [redacted]:

H_o: 3 month responder rate ≤ 75%

H_a: 3 month responder rate > 75%

11.1.4.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.1.4.3. Statistical Methods

ACUITY X4 Primary Effectiveness Endpoint 1 will be analyzed [redacted] Subjects eligible for this analysis includes all [redacted] subjects who are successfully implanted with an ACUITY X4 lead. Subjects with LV pacing threshold data in the programmed configuration collected at the 3-month follow-up visit will contribute data to the endpoint analysis.

[redacted]

Subjects that do not have LV pacing threshold data in the programmed configuration collected at the three month follow-up visit will be considered to have missing data. A tipping point analysis will be used to determine the potential effects subjects with missing data could have had on the results. The tipping point analysis will consider a range of possible responder rates in the subjects with missing data. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis rejected) to failing (null hypothesis not rejected).

11.1.5. ACUITY X4 Primary Effectiveness Endpoint 2

The second effectiveness endpoint for ACUITY X4 is pacing capture thresholds (PCT) in in the proximal zone (E2, E3, or E4) for [redacted]. This endpoint will be evaluated at 3 months post-implant.

Clustering electrodes on the spiral is expected to position at least one electrode adjacent to the myocardium. Physician investigators will therefore be instructed to use the "best" proximal electrode (E2, E3 or E4) as the cathode and the RV lead coil as the anode. For this endpoint "best" will be defined as the electrode with the lowest PCT without PNS. The PG may be used as an anode depending on the clinical scenario or physician preference. For this endpoint, responders will be defined as patients with PCT $\leq$ 2.5 V in the best proximal zone at 3 months post-implant.

11.1.5.1. Hypotheses

The following hypotheses will be used to evaluate Primary Effectiveness Endpoint 2 [redacted]

H_o: 3 month responder rate $\leq$ 75%

H_a: 3 month responder rate > 75%

11.1.5.2. Sample Size

[redacted]:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted]

11.1.5.3. Statistical Methods

ACUITY X4 Primary Effectiveness Endpoint 2 will be analyzed when the last 3-month follow-up visit [redacted] is completed. All [redacted] subjects who are successfully implanted with an ACUITY X4 spiral lead [redacted] eligible for inclusion in this analysis. Subjects with a best proximal zone LV pacing threshold measurement collected at the 3-month follow-up visit will contribute data to the endpoint analysis.

[redacted]

Subjects that do not have a best proximal zone LV pacing threshold measurement collected at the three month follow-up visit will be considered to have missing data. A tipping point analysis will be used to determine the potential effects subjects with missing data could have had on the results. The tipping point analysis will consider a range of possible responder rates that could have been observed in the subjects with missing data. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis rejected) to failing (null hypothesis not rejected).

11.1.6. ACUITY X4 Secondary Effectiveness Endpoint 1

The first secondary effectiveness endpoint for ACUITY X4 is sensed amplitudes in the programmed configuration. This endpoint will be evaluated at 3 months post-implant.

11.1.6.1. Hypotheses

The following hypotheses will be used to evaluate the sensed amplitude Secondary Effectiveness Endpoint 1 [redacted]:

H_o: The three -month mean R-wave amplitude is $\leq$ 3.0 mV

H_a: The three -month mean R-wave amplitude is > 3.0 mV

11.1.6.2. Sample Size

[redacted]:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted].

11.1.6.3. Statistical Methods

ACUITY X4 Secondary Effectiveness Endpoint 1 will be analyzed when the last 3-month [redacted] follow-up visit is complete. This analysis will include [redacted] subjects with an ACUITY X4 LV sensed amplitude measurement at three months, and the analysis will be done [redacted] Sensed amplitude measurements in the programmed configuration from the three-month follow-up visit will be analyzed using a one-sided t-test with an alpha of 2.5%. A histogram of three month LV sensed amplitudes in the programmed configuration will also be provided.

11.1.7. ACUITY X4 Secondary Effectiveness Endpoint 2

The second secondary effectiveness endpoint for ACUITY X4 is pacing impedances in the programmed configuration. This endpoint will be evaluated at 3 months post-implant.

11.1.7.1. Hypotheses

The following hypotheses will be used to evaluate the pacing impedance Secondary Effectiveness Endpoint for [redacted]:

H_o: The three -month mean LV lead impedance is ≤ 300 Ω

H_a: The three -month mean LV lead impedance is > 300 Ω

11.1.7.2. Sample Size

[redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

11.1.7.3. Statistical Methods

ACUITY X4 Secondary Effectiveness Endpoint 2 will be analyzed when the last 3-month follow-up visit [redacted] is complete. This analysis will include all [redacted] patients with an ACUITY X4 LV pacing impedance at three months, and the analysis will be done [redacted] LV lead pacing impedance measurements in the programmed configuration from the three-month follow-up visit will be analyzed using a one-

sided t-test with an alpha of 2.5%. A histogram of three month LV pacing impedances in the programmed configuration will also be provided.

11.1.8. ACUITY X4 Ancillary Analyses

11.1.8.1. ACUITY X4 Ancillary Safety Objective

The ACUITY X4 Ancillary Safety Objective will be used to prospectively determine the chronic five year complication-free rate of the ACUITY X4 LV lead. [redacted].

11.1.8.2. ACUITY X4 Ancillary Data Collection

The following data will be collected and summarized:

- Implant success
- Lead measurements in all tested configurations
- Dislodgment rate (post-implant)
- Skin-to-skin time
- Feedback from the site investigator regarding final ACUITY X4 programmed configuration if the physician chooses a configuration other than the best configuration; (best electrode is the one that has the lowest threshold without phrenic nerve stimulation (PNS). In the event of a "tie" for best electrode, the investigator should use their medical judgment to select the best)
- ACUITY X4 Lead placement time
- Interoperative repositioning and rationale for selection of multiple veins/branches
- Method of lead delivery (inner or outer sheath)
- Vein used to implant LV lead – Right-sided vs. left-sided and axillary, cephalic, or subclavian

11.2. *RELIANCE 4-FRONT Endpoints*

11.2.1. RELIANCE 4-FRONT Primary Safety Endpoint 1

Safety of the RELIANCE 4-FRONT Leads will be evaluated by the lead-related complication-free rate (CFR) from lead implant through the 3-month follow-up visit, based on complications that are related to the RELIANCE 4-FRONT Lead. Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury or death. Lead-related adverse events are further defined in Section 19.3 and lead-related complications are further defined in Section 19.3.1.

Lead-related complications associated with attempted RELIANCE 4-FRONT Lead implants will count toward this safety endpoint.

11.2.1.1. Hypotheses

The following hypotheses will be used to evaluate the RELIANCE 4-FRONT Primary Safety Endpoint 1 [redacted]:

H_o: The lead-related complication-free rate from implant to 3 months ≤ 93.0%

H_a: The lead-related complication-free rate from implant to 3 months > 93.0%

[redacted]

11.2.1.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.2.1.3. Statistical Methods

Data from all subjects implanted or attempted with a RELIANCE 4-FRONT lead will be eligible for inclusion in the endpoint analysis. All RELIANCE 4-FRONT leads [redacted] will be pooled for this analysis.

The lead-related complication-free rate from date of implant (or date of attempt, for leads attempted but not implanted) through 91 days post-implant will be calculated using Kaplan-Meier methodology. The 95% one-sided lower pointwise confidence limit of the complication-free rate will be calculated via log-log methodology for all eligible subjects contributing to the analyses and compared to the performance goal of 93%. If the lower confidence limit exceeds 93%, the null hypothesis will be rejected.

Each lead's exact follow-up time in the 91 days post-implant will be included in the analysis via Kaplan-Meier methodology. The leads that fail to reach 91 days of follow-up (without

experiencing an endpoint event prior to their end of follow-up in the period) will be censored at the time of their end of follow-up in the period. Because non-informative censoring cannot be assumed for these leads, a tipping point analysis will be performed to determine the potential effects these censored leads could have on the results if full information on each lead was present. The tipping point analysis will assign each lead that was censored prior to 91 days as either having or not having an endpoint event. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis) to failing (null hypothesis rejected). An exact binomial test will be performed for the tipping point analysis.

11.2.2. RELIANCE 4-FRONT Primary Safety Endpoint 2

To satisfy the safety assessment requirements of the US Food and Drug Administration (FDA), safety of the RELIANCE 4-FRONT Leads will also be evaluated by the lead-related CFR from three months post-implant through 24 months post implant based on complications that are related to the RELIANCE 4-FRONT Lead during that period. The same definition of lead-related complication will be used for both RELIANCE 4-FRONT Primary Safety Endpoint 1 and Primary Safety Endpoint 2.

11.2.2.1. Hypotheses

The following hypotheses will be used to evaluate RELIANCE 4-FRONT Primary Safety Endpoint 2 [redacted]:

H_o: The lead-related complication-free rate from 3 to 24 months ≤ 94%

H_a: The lead-related complication-free rate from 3 to 24 months > 94%

11.2.2.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.2.3. Statistical Methods

Data from all RELIANCE 4-FRONT leads that have been followed for at least [redacted] days post-implant at the time of endpoint analysis will be eligible for inclusion in the endpoint analysis. All RELIANCE 4-FRONT leads [redacted] will be pooled for this analysis.

The lead-related complication-free rate from [redacted] days through [redacted] days post-implant will be calculated using Kaplan-Meier methodology. The 95% one-sided lower pointwise confidence limit of the complication-free rate will be calculated via log-log methodology for all eligible subjects and compared to the performance goal of 94%. If the lower confidence limit exceeds 94%, the null hypothesis will be rejected.

Each lead's exact follow-up time in the period between [redacted] days post-implant will be included in the analysis due to the rate being calculated via Kaplan-Meier methodology. The leads that reach [redacted] of follow-up but fail to reach [redacted] of follow-up (without experiencing an endpoint event in the period prior to their end of follow-up) will be censored at the time of their end of follow-up in the period. Because non-informative censoring cannot be assumed for these leads, a tipping point analysis will be performed to determine the potential effects these censored leads could have on the results if full information on each lead was present. The tipping point analysis will assign each lead that was censored between the [redacted] post-implant as either having or not having an endpoint event. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis) to failing (null hypothesis rejected). An exact binomial test will be performed for the tipping point analysis.

11.2.4. RELIANCE 4-FRONT Secondary Safety Endpoint

The purpose of this endpoint is to confirm that the RELIANCE 4-FRONT lead and its associated PG system have the ability to appropriately sense and detect VT/VF. Historically, this endpoint has been used to evaluate system performance; the lead is part of the system and therefore will be evaluated in this study. Subjects will not be required to undergo induction testing. Those subjects with a RELIANCE 4-FRONT lead that undergo induction testing within 30 days of implant, per the discretion of the investigator, will be included in the analysis and the time to detection of VT/VF will be measured.

11.2.4.1. Hypotheses

The time it takes for the device to detect VT/VF will be compared to performance goal of 4.5 seconds, [redacted].

H_o: Induced mean VT/VF detection time ≥ 4.5 seconds

H_a: Induced mean VT/VF detection time < 4.5 seconds

11.2.4.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

11.2.4.3. Statistical Methods

Data from all subjects with a RELIANCE 4-FRONT lead that have undergone an induction test within 30 days of implant will contribute to the analysis of this endpoint.

If multiple tests or multiple configurations are tested in the 30 day post-implant period, the last induction test in its final configuration will be used in the analysis. A one-sided one-sample t-test will be performed, using an alpha equal to [redacted]. If the t-test is deemed to be inappropriate based on the data, then a data transformation or a non-parametric test will be performed. If the p-value for the one-sided test is less than [redacted], the null hypothesis will be rejected.

11.2.5. RELIANCE 4-FRONT Primary Effectiveness Endpoint

Effectiveness of the RELIANCE 4-FRONT Leads will be established by demonstrating that the leads provide clinically acceptable pacing thresholds at a 0.5 ms pulse width at three months post implant. [redacted].

11.2.5.1. Hypotheses

The following hypotheses will be used to evaluate the RELIANCE 4-FRONT Primary Effectiveness Endpoint [redacted]:

H_o: The pacing threshold at 0.5 ms at three months post-implant $\geq$ 1.5 V

H_a: The pacing threshold at 0.5 ms at three months post-implant < 1.5 V

11.2.5.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.2.5.3. Statistical Methods

All RV lead pacing threshold data from subjects with the RELIANCE 4-FRONT lead collected at the 3-month follow-up visit will be included in the endpoint analysis.

A one-sided one-sample t-test will be performed, using an alpha equal to [redacted]%. If the t-test is deemed to be inappropriate based on the data, then a data transformation or a non-parametric test will be performed. If the p-value for the one-sided test is less than [redacted]%, the null hypothesis will be rejected.

Subjects that do not have pacing threshold data collected at the three month follow-up visit will not contribute any data to the endpoint analysis. A tipping point analysis will be used to determine the potential effects these subjects could have had on the results if they would have had endpoint data for inclusion in the analysis. The tipping point analysis will consider a range of possible mean pacing threshold values that could have been observed in the subjects with missing data. The observed mean and the possible mean from the subjects with missing data will be pooled for the tipping point analysis. The tipping point will be determined by the possible mean value ([redacted]) at which the endpoint results turn from passing (null hypothesis rejected) to failing (null hypothesis failed to be rejected).

11.2.6. RELIANCE 4-FRONT Secondary Effectiveness Endpoint 1

The purpose of this secondary effectiveness endpoint is to establish that the RELIANCE 4-FRONT Lead leads provide clinically acceptable sensing amplitudes at three months post implant. [redacted].

11.2.6.1. Hypotheses

The following hypotheses will be used to evaluate Secondary Effectiveness Endpoint 1 for [redacted]:

H_o: R-wave sensed amplitude at three months post-implant ≤ 5 mV

H_a: R-wave sensed amplitude at three months post-implant > 5 mV

11.2.6.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.2.6.3. Statistical Methods

All R-wave sensed amplitude data collected at the 3-month follow-up visit will be included in the endpoint analysis.

A one-sided one-sample t-test will be performed, using an alpha equal to [redacted]%. If the t-test is deemed to be inappropriate based on the data, then a data transformation or a non-parametric test will be performed. If the p-value for the one-sided test is less than [redacted]%, the null hypothesis will be rejected.

11.2.7. RELIANCE 4-FRONT Secondary Effectiveness Endpoint 2

The purpose of this secondary effectiveness endpoint is to establish that the RELIANCE 4-FRONT Lead provides clinically acceptable pacing impedance at three months post-implant. [redacted].

11.2.7.1. Hypotheses

The following hypotheses will be used to evaluate the Secondary Effectiveness Endpoint 2 [redacted]:

H_o: Pacing impedance ≤ 300 Ω, or pacing impedance ≥ 1200 Ω

H_a: 300 Ω < Pacing impedance < 1200 Ω

11.2.7.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

11.2.7.3. Statistical Methods

Endpoint analysis will be performed [redacted] 4-FRONT [redacted]. Leads will not be pooled for the hypothesis testing, due to expected differences in performance for this endpoint between the active and passive fixation leads. Results will be presented split by fixation type, but will not be split by coil type. Two one-sided t-tests (TOST) will be performed, using an alpha equal to [redacted]% for each test. If the TOST is deemed to be inappropriate based on the data, a data transformation or a non-parametric test will be performed. If both of the p-values for the two one-sided tests are less than [redacted]%, the null hypothesis will be rejected.

11.2.8. RELIANCE 4-FRONT Secondary Effectiveness Endpoint 3

The purpose of this secondary endpoint is to confirm that the RELIANCE 4-FRONT lead and its associated PG system have the ability to successfully convert VT/VF. Historically, this endpoint has been used to evaluate system performance; the lead is part of the system and therefore will be evaluated in this study. Subjects will not be required to undergo induction testing. Those subjects that undergo induction testing within 30 days of implant, per the discretion of the investigator, will be included in the analysis and the time to detection of VT/VF will be measured. Success will be considered if the device converts the subject's last induced episode in its final configuration without the need for external defibrillation.

11.2.8.1. Hypotheses

The percent of successful VT/VF conversions with a RELIANCE 4-FRONT lead will be compared to a performance goal of 93%, [redacted]. The null hypothesis will therefore be rejected in favor of the alternative if the upper confidence limit of the observed percent of successful conversions is greater than 93%. The conversion will be considered successful if the device converts the subject without the need for external defibrillation. [redacted]

H_o: Percent of successful conversion ≤ 93%

H_a: Percent of successful conversion > 93%

11.2.8.2. Sample Size

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

11.2.8.3. Statistical Methods

All subjects with a RELIANCE 4-FRONT lead that undergo an induction test within 30 days of implant will contribute to the analysis of this endpoint. If multiple tests or multiple configurations are tested in the 30 day post-implant period, the last induction test in its final configuration will be used in the analysis. A one-sided exact binomial test will be performed on all subjects with induction data (regardless of lead fixation or coil type) and the resulting lower exact (Clopper-Pearson) confidence interval will be calculated, using an alpha equal to [redacted]%. If the lower one-sided 95% confidence limit for the conversion rate is greater than 93%, the null hypothesis will be rejected.

11.2.9. RELIANCE 4-FRONT Ancillary Analyses

11.2.9.1. RELIANCE 4-FRONT Ancillary Safety Objective

The RELIANCE 4-FRONT Ancillary Safety Objective will be used to prospectively determine the chronic five year complication-free rate of the RELIANCE 4-FRONT RV lead. The overall sample size required for this endpoint is greater than the sample size of this NAVIGATE X4 study. The remaining leads will be enrolled under a separate post-market approval study protocol. Data from this study and data from the post-approval study protocol will be pooled for purposes of analysis.

11.2.9.2. Additional Analyses for RELIANCE 4-FRONT

To assess the long term performance of electrical measurements, pacing threshold, sensed amplitude, and pacing impedance at 24 months will be summarized using descriptive statistics. Spontaneous VT/VF events will also be summarized with descriptive statistics.

11.3. *General Statistical Methods*

All sample size calculations were performed and all statistical analyses will be done with SAS version 9.1 or higher.

11.3.1. Study Success Criteria

The study success will be determined [redacted] for ACUITY X4 and RELIANCE 4-FRONT. Each study will be considered successful if all primary endpoints specific to that lead are passed

11.3.2. Analysis Sets

The following analysis sets will be used for each endpoint. Note that for all analyses, the final lead implanted or attempted from the initial procedure will contribute to the analysis.

Endpoint	Analysis Sets
ACUITY X4 Primary Safety Endpoint	All subjects implanted or attempted with ACUITY X4
ACUITY X4 Primary Effectiveness Endpoint 1	All ACUITY X4 leads with measurements taken at the three-month follow-up visit

Endpoint	Analysis Sets
ACUITY X4 Primary Effectiveness Endpoint 1	All ACUITY X4 [redacted] leads with measurements taken at the three-month follow-up visit
ACUITY X4 Secondary Effectiveness Endpoints 1 & 2	All ACUITY X4 leads with measurements taken at the three-month follow-up visit
ACUITY X4 Ancillary Safety Objective	Analysis will not be performed at the time of report submission since 60-month data from this study will be pooled with data from an ACUITY X4 Post-Market Approval Study
RELIANCE 4-FRONT Primary Safety Endpoint 1	All subjects implanted or attempted with RELIANCE 4-FRONT
RELIANCE 4-FRONT Primary Safety Endpoint 2	All subjects implanted with RELIANCE 4-FRONT that have been followed for at least [redacted] days post-implant
RELIANCE 4-FRONT Secondary Safety Endpoint	All subjects implanted with RELIANCE 4-FRONT that undergo an induction test within 30 days of implant will contribute to the analysis of this endpoint
RELIANCE 4-FRONT Ancillary Safety Objective	Analysis will not be performed at the time of report submission since 60-month data from this study will be pooled with data from a RELIANCE 4-FRONT Post-Market Approval Study
RELIANCE 4-FRONT Primary Effectiveness Endpoint	All RELIANCE 4-FRONT leads with measurements taken at three month follow-up visit
RELIANCE 4-FRONT Secondary Effectiveness Endpoints 1 &2	All RELIANCE 4-FRONT leads with measurements taken at three month follow-up visit
RELIANCE 4-FRONT Secondary Effectiveness Endpoint 3:	All subjects implanted with RELIANCE 4-FRONT that undergo an induction test within 30 days of implant will contribute to the analysis of this endpoint

11.3.3. Control of Systematic Error/Bias

Selection of subjects for enrollment will be made from the Investigator's usual patient load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study.

11.3.4. Control of Type-I Error

Control of type-I Error will be handled separately for ACUITY X4 and RELIANCE 4-FRONT.

ACUITY X4

Each primary endpoint can be tested at the significance level specified in Section 11.1 ([redacted]). For each lead, due to the requirement that each applicable endpoint must be passed, each applicable endpoint can be tested at the specified significance level while still maintaining the overall type-I error level at no greater than [redacted]%.This follows the methodology of the Intersection-Union Test (IUT).

If all primary endpoints are passed, then a gating approach will be employed to test the following secondary endpoints in this order:

- Secondary Effectiveness Endpoint 1
- Secondary Effectiveness Endpoint 2

RELIANCE 4-FRONT

Each primary endpoint can be tested at the significance level of [redacted]% while still maintaining the overall type-I error level of no more than [redacted]%. This follows the methodology of the Intersection-Union Test (IUT). If all primary endpoints are passed, then a gating approach will be employed to test the following secondary endpoints in this order:

- Secondary Effectiveness Endpoint 1
- Secondary Effectiveness Endpoint 2
- Secondary Safety Endpoint
- Secondary Effectiveness Endpoint 3

11.3.5. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 20% of the maximum number of [redacted] of this protocol, without approval from Boston Scientific. Similarly, and with the same rationale, one center will not be authorized to enroll more than 20% of the maximum number of [redacted] subjects [redacted] this protocol, without approval from Boston Scientific.

11.4. *Data Analyses*

11.4.1. Interim Analyses

Analyses of adverse events and device deficiencies will occur at frequent intervals during the course of the study. Results of these analyses will be reviewed by the Boston Scientific Medical Safety Group to evaluate the safety of the subjects under study.

A futility analysis for each investigational lead – ACUITY X4 and RELIANCE 4-FRONT – will be conducted for each effectiveness endpoint. The futility analyses for ACUITY X4 leads will occur at the point at which [redacted] subjects have been enrolled for 3 months. [redacted] If a futility analysis reveals that the conditional power to pass an effectiveness endpoint is sufficiently low (less than 20%), Boston Scientific may consider terminating enrollment for one (or both) leads. To reduce the potential for biasing the results, the futility analyses will be performed by a BSC statistician independent from the NAVIGATE X4 Study.

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness. The hypothesis test for each endpoint will be performed when all applicable data for that endpoint has been collected.

11.4.2. Pooling Analyses

11.4.2.1. RELIANCE 4-FRONT Pooling of Cohorts

It is expected that results will not differ [redacted] for any endpoint, with the exception of Secondary Effectiveness Endpoint 2. In order to confirm the poolability for each endpoint, a pooling analysis will be performed. Specifically, a likelihood ratio test from a regression model will be conducted. The type of regression model used for each of the following endpoints is as follows:

- Primary Safety Endpoint 1 (CFR from Implant to 3 Months): Logistic Regression
- Primary Safety Endpoint 2 (CFR from 3 to 24 Months): Logistic Regression
- Secondary Safety Endpoint (Detection of VT/VF): Linear Regression
- Primary Effectiveness Endpoint (Pacing Threshold at 3 Months): Linear Regression
- Secondary Effectiveness Endpoint 1 (Sensed Amplitude at 3 Months): Linear Regression
- Secondary Effectiveness Endpoint 3 (VT/VF Shock Conversion): Logistic Regression

The regression model will include additional baseline covariates to attempt to adjust for any imbalances between baseline data. The following baseline covariates will be considered: age, gender, etiology, CRT-D indication, LVEF, NYHA classification, medications, arrhythmia history, associated diseases/risk factors, height, weight and geography. [redacted].

[redacted]

11.4.2.2. ACUITY X4 Pooling of Cohorts

It is expected that results will not differ [redacted] for any endpoint, with the exception of Secondary Effectiveness Endpoint 2. In order to confirm the poolability for each endpoint, a pooling analysis will be performed. Specifically, a likelihood ratio test from a regression model will be conducted. The type of regression model used for each of the following endpoints is as follows:

- Primary Safety Endpoint (CFR from Implant to 6 Months): Logistic Regression
- Primary Effectiveness Endpoint 1 (Pacing Threshold at 3 Months, programmed): Logistic Regression
- Primary Effectiveness Endpoint 2 (Pacing Threshold at 3 Months, best proximal): Logistic Regression
- Secondary Effectiveness Endpoint 1 (Sensed Amplitude at 3 Months): Linear Regression
- Secondary Effectiveness Endpoint 2 (Pacing Impedance at 3 Months): Linear Regression

The regression model will include additional baseline covariates to attempt to adjust for any imbalances between baseline data. The following baseline covariates will be considered: age, gender, etiology, CRT-D indication, LVEF, NYHA classification, medications, arrhythmia history, associated diseases/risk factors, height, weight and geography. [redacted].

[redacted]

11.4.2.3. Pooling of Geographies

It is expected that results will not differ by geographic regions for any of the endpoints for either lead. In order to confirm the poolability of the data from the geographic regions for each endpoint, a pooling analysis will be performed. Specifically, a likelihood ratio test from a regression model will be conducted. [redacted]

11.4.2.4. Pooling of investigational centers

Center-to-center heterogeneity will be assessed for each endpoint by performing random effects regression analyses. Centers with less than five enrollments will be combined to form "supercenters". Small centers will be combined until the newly created supercenter has five enrollments, and then a new supercenter will be created. The following regression models for each of the following endpoints will be used:

<u>ACUITY X4</u>

- Primary Safety Endpoint (CFR from Implant to 6 Months): Random Effects Logistic Regression
- Primary Effectiveness Endpoint 1 (Pacing Threshold at 3 Months, programmed): Random Effects Logistic Regression
- Primary Effectiveness Endpoint 2 (Pacing Threshold at 3 Months, best proximal): Random Effects Logistic Regression
- Secondary Effectiveness Endpoint 1 (Sensed Amplitude at 3 Months): Random Effects Linear Regression
- Secondary Effectiveness Endpoint 2 (Pacing Impedance at 3 Months): Random Effects Linear Regression

<u>RELIANCE 4-FRONT</u>

- Primary Safety Endpoint 1 (CFR from Implant to 3 Months): Random Effects Logistic Regression

- Primary Safety Endpoint 2 (CFR from 3 to 24 Months): Random Effects Logistic Regression
- Secondary Safety Endpoint (Detection of VT/VF): Random Effects Linear Regression
- Primary Effectiveness Endpoint (Pacing Threshold at 3 Months): Random Effects Linear Regression
- Secondary Effectiveness Endpoint 1 (Sensed Amplitude at 3 Months): Random Effects Linear Regression
- Secondary Effectiveness Endpoint 2 (Pacing Impedance at 3 Months): Random Effects Linear Regression
- Secondary Effectiveness Endpoint 3 (VT/VF Shock Conversion): Random Effects Logistic Regression

Investigational center will be added into the model as a random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of ■% will be used for each test. If it determined that the center random effect is significant for an endpoint, then the results from the random effects model for that endpoint will be presented. Regardless of the results of the random effects model, results by investigational center will be presented for each endpoint.

11.4.3. Subgroup Analyses

Analyses will be performed for each endpoint to determine whether significant differences exist in endpoint results between subgroups. Results will be presented for each subgroup, regardless of whether significant differences exist between the subgroups. The list of baseline covariates (with applicable subgroups in parentheses) includes, but is not necessarily limited to:

- Sex (Female vs. Male)
- Geography (International vs. United States)
- Age (< 65 years vs. ≥ 65 years)
- NYHA Class
- LVEF (< 25% vs. ≥ 25%)
- QRS width (< 150 ms vs. ≥ 150 ms)
- Bundle Branch Block Morphology (LBBB vs. non-LBBB)

For ACUITY X4, the following additional baseline covariates will be assessed:

- Spiral length (Short vs. Long)
- Lead shape (Spiral vs. Straight)

For RELIANCE 4-FRONT, the following additional baseline covariates will be assessed:

- Fixation type (Active vs. Passive)
- Coil type (Dual vs. Single)

The baseline covariate will be added to a univariate regression model and a test for significance at the [redacted]% level will be performed. The regression models used for each endpoint will be identical to those specified in Section 11.4.2.1.

In addition to subgroup analyses, descriptive statistics of patient demographic and baseline characteristics will be presented for each subgroup listed in this section. Descriptive statistics will also be presented for the overall study population.

11.4.4. Multivariate Analyses

Univariate analyses of various baseline covariates and their relationship to each endpoint are outlined in Section 11.4.3. For each endpoint, all baseline characteristics found to be significantly associated with the outcome will be included as covariates in a multivariate regression model. The impact of each baseline characteristic's subgroups will be presented along with the multivariate model results.

11.4.5. Early Projection of Ancillary Safety Endpoint Results

At the time of the submission of the Clinical Report for each lead ([redacted] it is desired to obtain an estimate of the chronic complication-free rate at 60-months. To obtain such an estimate, two methods will be employed:

1. [redacted]
2. [redacted]

Through the interpretation of the results of both analysis methods, an understanding of the expected 60-month results will be obtained.

11.4.6. Accuracy of Projection Estimates for Long-term Lead-Related Complication-Free Rates

As stated in the previous section, parametric survival models (such as the Weibull and log-logistic) provide the ability to project survival curves and yield survival estimates beyond the evaluation time period. The objective of this ancillary analysis is to evaluate the ability of these parametric survival models to provide accurate long-term estimates using data collected through a shorter-term follow-up. This analysis will be performed separately for ACUITY X4 and RELIANCE 4-FRONT. Actual complication rates observed at long-term time points (e.g. 24, 36,

48, 60 months) will be compared to the corresponding projected/estimated complication rates produced using data collected through earlier time points (e.g. 3, 6, 12 months).

The risk period for the events of interest for these analyses may begin at implant or at some later time point (e.g. 3 months), depending on the type of event being considered. For example, a survival projection for dislodgments may start at implant, while a survival projection for chronic lead fractures may start at 3 months.

A parametric survival analysis can provide unreliable estimates if an insufficient sample size or insufficient number of events is present. [redacted]

11.4.7. Changes to Planned Analyses

Any changes to the planned statistical analyses outlined in this protocol will be documented in the statistical analysis plan and/ or clinical study reports along with a reason for the deviation.

12. DATA MANAGEMENT

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSC or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

12.2. *Data Retention*

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with International Conference on Harmonisation (ICH)/ Good Clinical Practice (GCP) guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for

a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13. AMENDMENTS

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

14. DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the EDC system. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions put into place by the sponsor (including notification, center re-training, or discontinuation).

15. INVESTIGATIONAL DEVICE/ EQUIPMENT ACCOUNTABILITY

This section applies to sites in the US, as the only geography with investigational devices/ equipment. The investigational products used in the NAVIGATE X4 Study must be securely maintained, controlled, and used only as a part of this clinical study. Investigational products in this study include the AUTOGEN X4 CRT-D, ACUITY X4 quadripolar coronary venous leads, and associated flushing tool (tracked only if used as separate accessory Model 4604), connector tool (tracked only if used as separate accessory Model 4625) and accessory slit suture sleeve (Model 4603), the RELIANCE 4-FRONT defibrillator leads and associated accessory slit suture sleeve, (Model 6403), as well as 2909 MAU, 2868 software application, and 3140 ZWT. Current Boston Scientific processes will be used to track investigational device/ equipment allocations during the study.

Boston Scientific shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following:

- Date of receipt
- Identification of each investigational device/piece of equipment (model number and serial or lot number)
- Expiration date, as applicable
- Date or dates of use (for implantable devices only, not PRM)
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

Written procedures may be required by national regulations.

Upon completion of enrollment into the NAVIGATE X4 Clinical Study, or as directed by Boston Scientific, all unused investigational AUTOGEN X4 CRT-Ds, ACUITY X4 Leads, ACUITY X4 Connector Tool, ACUITY X4 Flushing Tool/ Wire Guide, RELIANCE 4-FRONT Leads and accessory suture sleeves must be returned to Boston Scientific.

Also, at such time that the 2909 MAU, 2868 software application, and 3140 ZWT are approved for commercial use, or as directed by Boson Scientific, the clinical 3120 Zoom LATITUDE PRM must be returned to Boston Scientific.

16. COMPLIANCE

16.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155:2011, relevant parts of the ICH Guidelines for GCP, relevant parts of the Code of Federal Regulations (CFR), and ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any

conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device/ equipment are used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.

- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

16.4. *Sponsor Responsibilities*

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

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance

- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

17. MONITORING

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. POTENTIAL RISKS AND BENEFITS

18.1. *Anticipated Adverse Events*

Subjects participating in this study are subject to the same risks shared by all patients undergoing implantation of a CRT-D system.

Based on the literature and on pulse generator implant experience, Table 14 includes an alphabetical list of the possible adverse events associated with implantation of a pulse generator and/or lead system.

Table 14: Potential Adverse Events for Pulse Generator and/ or Lead System Implants

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Acceleration of arrhythmias	Incisional pain

Table 14: Potential Adverse Events for Pulse Generator and/ or Lead System Implants

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Adverse reaction to procedure (e.g., bradycardia, general, respiratory, hypotension)	Incomplete lead connection with pulse generator
Air embolism	Infection including endocarditis
Allergic reaction	Insulating myocardium during defibrillation with internal or external paddles
Arterial damage with subsequent stenosis	Lead dislodgment
Bleeding	Lead fracture
Breakage/ failure of the implant instruments	Lead insulation breakage or abrasion
Cardiac perforation	Lead perforation
Cardiac tamponade	Lead tip deformation and / or breakage
Chronic nerve damage	Local tissue reaction
Component failure	Loss of capture
Conductor coil fracture	Malignancy or skin burn due to fluoroscopic radiation
Coronary venous spasm	Myocardial necrosis
Death	Myocardial trauma (e.g.,irritability,injury, tissue damage, valve damage)
Electrolyte imbalance/ dehydration	Myopotential sensing
Elevated thresholds	Oversensing / undersensing
Erosion	Pacemaker-mediated tachycardia (PMT)
Excessive fibrotic tissue growth	Pericardial rub, effusion
Extracardiac stimulation (muscle/ nerve stimulation)	Pneumothorax
Failure to convert an induced arrhythmia	Pulse generator migration
Fluid accumulation	Shunting current during defibrillation with internal or external paddles
Foreign body rejection phenomena	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Formation of hematomas or seromas	Thrombus, thromboemboli
Heart block	Valve damage
Hemorrhage	Venous occlusion
Hemothorax	Venous trauma (e.g. perforation, dissection, erosion)
Inability to defibrillate or pace	Worsening heart failure
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	

*From the ACUITY X4, RELIANCE 4-FRONT Physician's Lead Manuals and/ or AUTOGEN, DYNAGEN, INOGEN, and ORIGEN CRT-D family (X4 and non-X4) Physician's Technical Manual.

In addition to the implantation of a PG and lead system, potential adverse events associated with implantation of a coronary venous lead system are listed in Table 15, below.

Table 15: Potential Adverse Events for Coronary Venous Lead Implants

List of potential adverse events for coronary venous lead system*	
Allergic reaction to the contrast media	Renal failure from contrast media used to visualize coronary veins
Prolonged exposure to fluoroscopic radiation	

*From the ACUITY X4 Physician's Lead Manuals and/ or AUTOGEN, DYNAGEN, INOGEN, and ORIGEN CRT-D family (X4 and non-X4) Physician's Technical Manual

Table 16: Potential Adverse Events for Implant of a Pulse Generator

List of potential adverse events for implant of a pulse generator*	
Dependency	Fear that shocking capability may be lost
Depression	Imagined shocking
Fear of premature battery depletion	Fear of device malfunction

*From the AUTOGEN, DYNAGEN, INOGEN, and ORIGEN CRT-D family (X4 and non-X4) Physician's Technical Manual

18.2. *Risks associated with Participation in the Clinical Study*

There are no specific tests outside of standard practice associated with this clinical study. Subjects who are implanted with an AUTOGEN X4 CRT-D in the US, have an added risk: ***Unavailability of a programmer/PRM with appropriate software to interrogate the AUTOGEN X4 device (this is in place until the programmer software is approved by FDA). Further, those US subjects implanted with an AUTOGEN X4 device will need a BSC representative at all follow ups as a programmer key (dongle key) is required to interrogate these devices until AUTOGEN devices are approved by FDA. This is the same risk shared by subjects in any new device IDE trial where only study programmers can interrogate the device.***

This information is also provided in Section 4.1.2.

18.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

18.4. *Anticipated Benefits*

There may be no benefit to the subject. However, subjects participating in clinical studies may have better outcomes than the general population. The subject may benefit from closer device follow up due to the clinical protocol schedule. Subjects may be followed more carefully and their status, as well as their PG and lead status is checked by various persons and systems:

Investigators, data coordinators, monitors and automatic warning systems in the clinical study database set to monitor the data as it is submitted to Boston Scientific.

18.5. *Risk to Benefit Rationale*

Risk management activities, including hazard analyses and fault tree analysis, have been performed on the ACUITY X4 leads, RELIANCE 4-FRONT leads and BSC X4 CRT-Ds to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and instructions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The hazard analysis has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the patient.

19. SAFETY REPORTING

19.1. *Definitions and Classification*

All Adverse Events reported to Boston Scientific during the study will be reviewed and adequately reported to comply with applicable regulations (ISO 14155: 2011 and/or 21 CFR Part 812). Investigators will be asked to classify whether an adverse event is considered serious or non-serious, whether it is anticipated or unanticipated (meets USADE/ UADE definition) as defined in Table 17 below, and whether it is considered device or procedure related, as defined in Section 19.2. Any event that is determined to be an unanticipated serious adverse device effect (USADE; ISO 14155: 2011) will also be considered an unanticipated adverse device effect (UADE; CFR Part 812), as defined in Table 17 below.

Table 17: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Table 17: Adverse Event Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812* **Note**: For US IDE studies only, otherwise remove UADE from table	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010* **Note**: For studies conducted outside the US only, otherwise remove USADE from table.	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: **EC**=Ethics Committee; **IRB**=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the NAVIGATE X4 Clinical Study. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 17 for AE definitions).

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 18 for the known risks associated with the study device(s).

19.2. *Relationship to Study Device(s) or Investigational Device Implant Procedure*

The Investigator must assess the relationship of the AE to the investigational devices (AUTOGEN X4, ACUITY X4, RELIANCE 4-FRONT) and to the implant procedure of the investigational devices as related or unrelated using the criteria in Table 18.

Table 18: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product or procedure related to the implant of the investigational device.
Related	• The adverse event is determined to be potentially related to the investigational product or procedure related to the implant of the investigational device, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product or procedure related to the implant of the investigational device, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

19.3. *Definition for Lead-related Adverse Events*

Those adverse events deemed related to one of the investigational leads, ACUITY X4 or RELIANCE 4-FRONT, the following definitions will also be applied. Lead-related adverse events include, but are not limited to the following, based on the Advamed Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads[37] and FDA Guidance Document[38]:

- Cardiac perforation requiring surgical intervention
- Cardiac perforation not requiring surgical intervention
- Conductor fracture/ helix damage
- Lead dislodgment
- Failure to capture
- Oversensing
- Failure to sense (undersensing)
- Insulation breach
- Abnormal pacing impedance
- Extracardiac stimulation

19.3.1. Definition for Lead-related Complication

Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention*, injury or death. *See definition for invasive intervention within the definition of "complication" in Table 20.

Lead-related complications associated with attempted ACUITY X4 and/ or RELIANCE 4-FRONT lead implants will count toward the respective safety endpoints. Lead-related adverse events that are not a complication will be counted as a complication if intravenous (IV) drug therapy is necessary to treat the event. IV drug therapy that occurs concomitant but unrelated to the lead-related adverse event will not be counted as a lead-related complication. Complications involving an ACUITY X4 and/ or RELIANCE 4-FRONT lead that occur as a result of a procedure unrelated to that ACUITY X4 and/ or RELIANCE 4-FRONT lead will not count toward the safety endpoints. Two examples of this scenario are 1) an ACUITY X4 and/or RELIANCE 4-FRONT lead dislodgement resulting from a repositioning of an RA lead and 2) an ACUITY X4 and/ or RELIANCE 4-FRONT lead dislodgement resulting from a CABG procedure.

19.4. *Adverse Event Classification*

Following receipt of adverse event information, the investigator's assessment of seriousness, relationship to the investigational device, and expectedness, will be reviewed and an internal BSC assessment will be documented. If the opinions between the investigator and BSC differ, both opinions will be reported, as appropriate.

In addition, case report forms are reviewed by internal BSC personnel and adverse events are assigned a type, classified as a clinical observation or a clinical complication, and coded for reporting purposes.

The adverse event is classified as one of the following Types:

Table 19: Adverse Event Types I-V to be Used for BSC AE Classification

Type	Description
Type I	Related to an investigational device, investigational procedure, investigational therapy, or procedure related to the implant of the investigational device.
Type II	Related to the protocol or procedures specifically related to protocol testing that is not standard of care.
Type III	Related to commercially available implanted components or commercially available features of an investigational device, or the procedure of a commercially available device
Type IV	Related to a change in the patient's condition or to therapies other than delivered by the implanted system.
Type V	Comments Only

The adverse event is classified as a clinical observation or complication, defined in Table 20.

Table 20: Definition of Observation and Complication

Clinical Event	Description
Observation	Adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or was resolved with no intervention or monitoring
Complication	An adverse event that resulted in: death, serious injury a, correction using invasive interventionb, or permanent loss of device functions. [a] Per 21 CFR 803.3: Serious injury means an injury or illness that: • Is life-threatening • Results in permanent impairment of a body function or permanent damage to a body structure, or • Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage [b] Invasive interventions are those in which treatment necessary to correct the adverse event is delivered by cutting or piercing of the skin or placing an instrument in a body cavity to provide therapy. Examples of invasive interventions (complication) include, but are not limited to: • Surgical revision of a lead • Electrophysiology study in which an ablation is performed • Angiogram in which angioplasty or stent placement is performed • Intravenous medications • Blood transfusions • Intubation to provide respiratory support • Chemical (pharmacologic) cardioversion with IV sedation (This is a complication due to the IV antiarrhythmic medication used for the cardioversion.) Invasive procedures that are purely diagnostic in nature should not be considered as a complication. Some examples of procedures that are invasive, but not considered to be an intervention include: • Blood draw for laboratory analysis • Cardiac catheterization in which pressures are recorded, but without therapeutic intervention • Electrophysiology study to map arrhythmias, but without therapeutic intervention • Transesophageal echo (TEE) • Electrical (external) cardioversion with IV sedation (the IV sedation used is for patient comfort and not part of the treatment) *See also definition for lead-related complication in Section 19.3.1.

19.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should

document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

In addition, any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate should be reported. Following receipt, the investigator's assessment is reviewed by internal BSC personnel. If the opinions between the investigator and BSC differ, both opinions will be reported, as appropriate.

NOTE: Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF and reported, as appropriate.

19.6. *Investigator Reporting Requirements*

The communication requirements for reporting adverse events, device deficiencies, failures, malfunctions, and product nonconformities to Boston Scientific are listed in Table 21.

Adverse events should always be reported through the EDC system for NAVIGATE X4. However, in case of any issues where an alternative method of reporting is necessary (i.e. the EDC is not available), please report the adverse event to Boston Scientific by sending the AE Notification Form via email to the following email address:

NAVIGATEX4Safety@bsci.com

Source documentation for UADE/USADE, SAE/SADE and BSC requested AE's can either be uploaded in the EDC system or sent via email, with the accompanying source document checklist to the following email address:

NAVIGATEX4Safety@bsci.com

Table 21: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect (UADE) / Unanticipated Serious Adverse Device Effect (USADE)	Complete AE eCRF page with all available new and updated information	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study

Table 21: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
	Provide all relevant source documentation (de-identified) for all subject deaths and any ACUITY X4 and/ or RELIANCE 4-FRONT lead-related events	• When documentation is available
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	• No later than 10 working days after becoming aware of the information • Reporting required through the end of the clinical study
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency section of the Adverse Event eCRF with all available new and updated information	• Within 1 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study

Abbreviations: **AE**=adverse event; **CRF**=case report form; **IDE**=Investigational Device Exemption; **UADE**=unanticipated adverse device effect

19.7. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating investigators, IRBs/ ECs, and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, of UADE and SAE as required by local/regional regulations.

19.8. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within two working days of center notification. The center's IRB must be notified of any deaths in accordance with that center's IRB policies and procedures.

Notification of death should include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the Principal Investigator or authorized sub-Investigator. A death narrative in the local language is acceptable, if accompanied by a translation in English (signed by an authorized translator). The death narrative must include all of the following, if available:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the pulse generator, lead/catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Device status and/or activity at the time of death
- Whether the subject had worsening heart failure
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)
- Investigator or co-Investigator signature and date

Any information listed above that is unavailable or unknown must be specified as unavailable or unknown, as applicable, in the narrative. Also submit the following documentation:

If the subject expired in the hospital:

- A copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the subject expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to Boston Scientific)
- Death certificate (if available)

Whenever possible, the PG should be interrogated. Investigational leads and related Boston Scientific system components (e.g., PGs) should be removed intact and returned promptly to Boston Scientific for analysis.

The NAVIGATE X4 Clinical Events Committee (CEC) must review information regarding subject deaths (see Section 21.1).

19.9. *Subject Death Classification*

The following definitions of each category, along with the Epstein article[39], are to be used by the investigator when completing the Death Information section.

I. **Primary Organ Cause** - The root problem that initiated the terminal event if multiple factors were involved, e.g., HF - primary, renal failure - secondary.

A. Cardiac

1. Arrhythmic

2. Pump Failure - Death occurring in a patient with severe heart failure, refractory to medical therapy, in whom death is anticipated within days to two months. Often such patients are referred for hospice care, comfort care is provided and aggressive treatment

is curtailed. The terminal event could be sudden and may be arrhythmic. This does not change the non-sudden, non-arrhythmic course that preceded the terminal event.

3. Ischemic

a. Acute MI - Symptoms compatible with an acute coronary syndrome (chest pain, acute dyspnea etc.), with evidence of myocardial necrosis as defined by:

i. creatinine kinase (CK) ≥ 2x upper limit of normal (ULN) and CK MB isoenzyme percent > ULN

ii. troponin level ≥ 2 x ULN

Patients with an acute coronary syndrome and diagnostic ST-T wave changes (>2 mm ST elevation in two contiguous leads) will be included if the death occurs prior to enzyme confirmation.

b. No Acute MI - Patient has not met the enzymatic or electrocardiographic criteria for an acute myocardial infarction. The testing was done and came back negative. For example, a patient who survives an unstable angina episode long enough to provide documentation that they did NOT have an MI, e.g., cardiac enzyme confirmation.

c. MI Unknown - Myocardial infarction suspected but data to prove or disprove are not available. Used to capture the patient who is suspected of having a probable MI but dies prior to the MI being documented. For example, chest pain > 20 minutes, or chest pain with a nondiagnostic EKG (LBBB), or chest pain of unknown duration.

4. Other Cardiac

5. Unknown

B. Noncardiac

C. Unknown

II. Temporal Course

A. Sudden - death that occurred within one hour of onset of symptoms

B. Non-Sudden - death that occurred greater than one hour of onset of symptoms

C. Unknown/Presumed Sudden - This category should be used for patients who were not expected to die of other causes, and were not witnessed at the time of death. There *must* be documentation of the patient's condition within 24 hours prior to the event and there should be no acute change in the patient's condition or circumstances leading up to the event. An example would be a stable patient who dies in his sleep. Patients can have worsening heart failure prior to the event and be included in this category, as long as the severity of heart failure does not fit the definition of death due to pump failure.

D. Unknown

III. Antecedent Worsening Heart Failure - Patients with signs or symptoms of worsening heart failure within the two weeks prior to death or the event that led to death (e.g. cardiac arrest and hypoxic encephalopathy from which the patient does not recover). In order to avoid recall bias,

there *must* be documentation of a clinical evaluation documenting worsening signs or symptoms or a change in medication recommended for symptoms of worsening heart failure.

A. N/A (Not Applicable)

B. Yes

C. No

D. Unknown - Insufficient information to determine state of heart failure at time of the event

IV. Death Witnessed - Someone witnessed the death event (in the same room or within earshot)

A. Yes

B. No

C. Unknown

V. Monitored - The patient rhythm at the onset of the terminal event (just prior to death) was documented. This may or may not be related to the actual cause of death. Device stored electrograms may not be used for this determination (depending on the study, i.e., heart failure).

A. Yes

1. **Ventricular Tachyarrhythmia**
2. **Bradyarrhythmia**

a. Sinus Bradyarrhythmia

b. High degree AV block with slow ventricular response

c. Asystole

3. **PEA (Pulseless Electrical Activity)**
4. **Other** (AF, SVT, sinus tachycardia, normal sinus rhythm)
5. **Unknown**

B. No

C. Unknown

VI. Operative Relationship

A. Pre-Operative - deaths that occur after the consent is signed, but before the procedure

B. Peri-Operative - deaths that occur ≤ 30 days post-op or prior to hospital discharge following any system related surgery including lead and pulse generator revisions.

C. Post-Operative - deaths that occur > 30 days post-implant or revision following discharge.

VII. Procedure Related - includes events during, or as a result of, events from pre-op anesthesia through leaving the OR suite, the EP lab, or an office visit.

A. Yes

B. No

C. Unknown

VIII. Investigation Related - related specifically to differences in procedure or necessary equipment used or implanted used solely for the new or investigational aspects of the study. An example would be a coronary sinus perforation from a new left ventricular pacing lead introduced via the coronary sinus.

A. Yes

B. No

C. Unknown

IX. Pulse Generator Related - includes events associated with pulse generator's ability to detect and treat an arrhythmia.

A. Yes

B. No - including events where initiating event was nonarrhythmic

C. Unknown

D. N/A

X. Lead/Catheter Related - includes events associated with the lead system's ability to detect and treat an arrhythmia.

A. Yes

B. No - including events where initiating event was nonarrhythmic

C. Unknown

20. INFORMED CONSENT

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall:

- be conducted by the Principal Investigator or designee authorized to conduct the process,

- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21. COMMITTEES

21.1. *NAVIGATE X4 Clinical Events Committee (CEC)*

A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates subject deaths reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported subject deaths from any cause.

Committee members will include a minimum of three practitioners with training in Electrophysiology (EP), and/ or Cardiology with the necessary therapeutic and subject matter

expertise to adjudicate subject deaths. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

22. SUSPENSION OR TERMINATION

22.1. *Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

22.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or IRB/ EC in the NAVIGATE X4 Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled at that center for a period beyond 3 months after center initiation, or if the center has multiple or severe protocol violations/non-compliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/ EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

23. PUBLICATION POLICY

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

24. ABBREVIATIONS AND DEFINITIONS

24.1. *Abbreviations*

Abbreviations used in this protocol are shown in Table 22.

Table 22: Abbreviations

Acronym/Abbreviation	Definition
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
BBB/LBBB	Bundle Branch Block/Left BBB
BSC	Boston Scientific
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CFR	Complication-free Rate
CRM	Cardiac Rhythm Management
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
DXA	Dexamethasone Acetate
EC/ IEC	Ethics Committee/ Institutional Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGM	Electrogram
EP	Electrophysiology
ETFE	Ethylene tetrafluoroethylene
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDMT	Guideline-directed medical therapy
HCP	Health Care Professional
HRS	Hearth Rhythm Society
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IUT	Intersection-Union Test
IROX	Iridium Oxide
ISO	International Standard Organization
LBBB	Left Bundle Branch Block
LOC	Loss of Capture
LV	Left Ventricle/ Ventricular
LVEF	Left Ventricular Ejection Fraction
MAU	Multiple Application Utility
MEDDEV	European Commission guidance on Medical

Table 22: Abbreviations

Acronym/Abbreviation	Definition
	Devices
MICS	Medical Implantable Communication Services
mV	Millivolts
Ω	Ohms
OPT	Optimal Pharmaceutical Therapy
PA	Posterior-Anterior
PCT	Pacing Capture Threshold
PG	Pulse Generator
PNS	Phrenic Nerve Stimulation
PRM	Programmer/ Recorder/ Monitor
PSA	Pacing System Analyzer
ePTFE	Expanded Polytetrafluoroethylene
RA	Right atrium/ atrial
RF	Radiofrequency
RV	Right ventricle/ ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TOST	Two one-sided t-tests
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
V	Volts
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation
ZWT	Zoom Wireless Transmitter

24.2. *Definitions of Terms*

Terms used in this protocol are defined in Table 23 below.

Table 23: Definitions

Term	Definition
ACUITY X4 Best Electrode	The best electrode configuration is the one that has the lowest threshold without phrenic nerve stimulation (PNS). In the event of a "tie" for best electrode, the investigator should use their medical judgment to select the best
Guideline-directed medical therapy (GDMT)	This term represents optimal medical therapy as defined by ACCF/AHA guidelines
Lead-related adverse event	Lead-related adverse events include, but are not limited to the following, based on the Advamed Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads: • Cardiac perforation requiring surgical intervention • Cardiac perforation not requiring surgical intervention • Conductor fracture/ helix damage • Lead dislodgment • Failure to capture • Oversensing • Failure to sense (undersensing) • Insulation breach • Abnormal pacing impedance • Extracardiac stimulation
Lead-related complication	Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury or death.
Pacing impedance	An assessment of the opposition to the flow of current by the pacing system; measured in ohms (Ω).
Pacing threshold	An assessment of the minimum electrical stimulation required to consistently initiate cardiac depolarization; measured in Volts (V).
Sensed amplitude	An assessment of how well the lead senses the heart's intrinsic electrical activity; measured in millivolts (mV).
Source Data (ISO 14155:2011)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study (Original records or certified copies).
Source Document (ISO 14155:2011)	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

25. INVESTIGATIONAL DEVICE DESCRIPTION

25.1. *ACUITY X4*

The ACUITY X4 lead family has the following characteristics:

- Coronary venous pace/sense lead—intended for chronic left ventricular pacing and sensing. This transvenous lead offers various pace/sense configurations depending upon the programming options of a compatible device; refer to the pulse generator manual for instructions. Placement is achieved by inserting the lead through the coronary sinus and placing it into a branch of the cardiac vasculature.
- Three tip configuration designs (straight tip, short tip spiral, long tip spiral)—intended to provide choices for a variety of patient anatomies. [redacted]
- IS4 four-pole connector—the industry standard connector to be used in conjunction with a compatible cardiac device with an IS4-LLLL port, where L indicates a connection to a low-voltage pace/sense electrode.
- IROX-coated electrodes—provide a pacing and sensing surface in the coronary venous system. The electrodes are coated with IROX (iridium oxide) to increase the microscopic surface area.
- 3D electrode spiral—the spiral model leads were designed to overcome challenges in mid-base (proximal) ventricular regions by clustering electrodes on the 3D spiral fixation, which is set back from the distal tip of the lead. The electrodes are spatially oriented on the spiral to increase the chance that at least one of the three electrodes will be placed adjacent to the myocardium in any coronary vasculature location.
- Lead body—the distal electrode (E1) is connected to the terminal pin by means of a coil conductor, while the three proximal electrodes (E2, E3, E4) are connected to the three terminal rings by means of three individual low voltage cable conductors. The coil conductor filars and the cables are sheathed in Ethylene tetrafluoroethylene (ETFE) insulation. The conductor separation insulation and the outer lead body insulation material are polyurethane in the proximal region and silicone in the distal region adjacent to the electrodes and spiral fixation.
- Protected IS4 terminal pin design—all proximal electrical connections occur within the terminal pin that fits safely inside the device header. There are no splice points in the lead body outside of the header. With this protected IS4 design, the absence of splice points in the lead body offers the following advantages:
  - protection from flex fatigue and fracture
  - protection from pulse generator-on-lead and lead-on-lead abrasion
  - protection from acute bending at splice points due to lead wrap
  - fewer connection points
- Distal tip—the distal tip is protected by silicone rubber to allow lead advancement through the coronary venous system.

- Steroid-eluting—upon exposure to body fluids, the steroid elutes from the drug collar near the distal end of the lead to help reduce tissue inflammation response. The steroid suppresses the inflammatory response believed to cause threshold rises typically associated with implanted pacing electrodes. The nominal dose and structure of the steroid are listed in the specifications included in the Physician's Lead Manual for ACUITY X4.
- Radiopaque suture sleeve—the radiopaque suture sleeve is visible under fluoroscopy and is used to secure, immobilize, and protect the lead at the venous entry site after lead placement. The window feature is designed to aid compression of the sleeve onto the lead during suturing.
- Tined fixation—silicone rubber tines located proximal to the distal electrode provide the option of passive fixation to the vasculature for all lead models.
- Spiral fixation—a distal, 3D spiral shape provides an additional or alternative passive fixation option for the spiral tip models.
- Fluoroscopic visibility—the platinum-iridium electrode design increases the visibility of the lead tip under fluoroscopy.
- Fluoroscopic marker—a radiopaque marker on the spiral models can be seen under fluoroscopy to indicate the approximate proximal end of the spiral fixation.
- Lubricious coating—the lead has a proprietary coating on the silicone distal region that makes the surface more lubricious. This reduces both the static and dynamic coefficients of friction, and makes the lead feel and handle like polyurethane while providing the flexibility of silicone.
- Over-the-Wire delivery method—the design consists of an open-lumen conductor coil that tracks over a guide wire.

25.2. *RELIANCE 4-FRONT*

25.2.1. Active Fixation

RELIANCE 4-FRONT leads with an active fixation electrode serving as the most distal tip electrode, consist of an IROX coated, platinum iridium alloy helix coil, which serves as the rate sensing bipolar cathode electrode and as a pacing tip. The distal tip electrode can be extended out of and retracted within the distal non-conductive rigid polymer components. A steroid drug collar impregnated with dexamethasone acetate (DXA) (an anti-inflammatory glucocorticoid) is placed at the distal end of the non-conductive housing. The distal tip contains a seal to limit the penetration of body fluids into the lumen during implant.

The distal tip electrode is connected to an inner, multi-filar, rotatable conductor coil insulated by the pace/sense lumen of trilumen silicone rubber tubing. A layer of expanded-polytetrafluoroethylene (ePTFE) tubing resides between the coil and the pace/sense lumen of the trilumen silicone tubing to aid rotational movement. The coil is continuous throughout the lead body, joining to the connector terminal.

The terminal pin is connected to the inner conductor coil and the assembly is free to rotate. The terminal assembly is hollow to allow for stylet passage. Rotation of the terminal pin transmits torque through the inner conductor coil to the distal tip electrode/helix. In this manner the helix

can be extended out of the distal tip housing allowing for fixation into cardiac tissue. The exposed surface area of the most distal tip electrode is approximately 5.7 mm^2. The helix may also be retracted into the distal tip housing if desired.

25.2.2. Passive Fixation

RELIANCE 4-FRONT leads with a passive fixation electrode serving as the most distal tip electrode, consist of a solid, IROX coated, platinum/iridium tip. It functions as the rate sensing bipolar cathode electrode and as a pacing tip. A steroid drug collar impregnated with DXA is placed at the distal end of the passive tip. Four molded elastomer tines adjacent to this tip electrode provide acute and chronic fixation. The exposed surface area of the distal electrode is approximately 3.5 mm^2.

25.2.3. Single Coil Electrode

RELIANCE 4-FRONT leads with a single coil electrode (intermediate distal electrode) consist of two distally located electrodes, connective elastomeric lead body sections, and one proximally located terminal, containing both high and low voltage connections. The intermediate distal electrode is a smooth surfaced platinum coated multi-filar composite round wire coil electrode. It functions as the electrocardiogram rate sensing/pacing anode, and cardioversion/defibrillation cathode. The conductor cable passes continuously through a tri-lumen extruded elastomer tubing to the connector terminal.

The distal tip electrode conductor coil proceeds to the inside tubing of the terminal body, and terminates with a tubular terminal connector pin located in the terminal connector assembly. This tubular connector pin allows a stylet wire to be inserted through the full length of the lead to the distal tip electrode as an aid in venous insertion and implant positioning.

25.2.4. Dual Coil Electrode

RELIANCE 4-FRONT leads with dual coil electrodes (intermediate distal electrode and most proximal electrode) consist of three distally located electrodes, connective elastomeric lead body sections, and one proximally located terminal, containing both high and low voltage connections. The intermediate distal electrode is a smooth surfaced platinum coated multi-filar composite round wire coil electrode. It functions as the electrocardiogram rate sensing/pacing anode, and cardioversion/defibrillation cathode. The most proximal electrode is also a smooth surfaced platinum coated multi-filar composite round wire coiled electrode. It functions as the cardioversion/defibrillation anode electrode. The proximal and distal conductor cables pass continuously through a tri-lumen extruded elastomer tubing to the connector terminal.

The distal tip electrode conductor coil proceeds to the inside tubing of the terminal body, and terminates with a tubular terminal connector pin located in the terminal connector assembly. This tubular connector pin allows a stylet wire to be inserted through the full length of the lead to the distal tip electrode as an aid in venous insertion and implant positioning.

25.2.5. Silicone Adhesive Backfilled Coils

RELIANCE 4-FRONT leads with dual coil electrodes contain an intermediate distal electrode and a most proximal electrode with silicone adhesive backfilled coils. The silicone adhesive backfill minimizes tissue ingrowth into the shocking coils.

25.2.6. ePTFE Covered Coils

RELIANCE 4-FRONT leads with a single coil electrode covered with expanded-polytetrafluoroethylene (ePTFE) contain an intermediate distal electrode covered with ePTFE, which allows rapid wetting by body fluids. RELIANCE 4-FRONT leads with dual coil electrodes covered with ePTFE contain an intermediate distal electrode and a most proximal electrode covered with surface treated ePTFE, which allows rapid wetting by body fluids. The ePTFE prevents tissue ingrowth into the shocking coils.

25.2.7. Iridium Oxide Coated Electrode

Iridium Oxide (IROX) has been added to the active fixation helix and the passive fixation tip of the RELIANCE 4-FRONT Lead. An IROX coating creates a high electrochemical surface area to reduce afterpotential (polarization) and pacing thresholds as well as improve sensing performance.

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