Protocol & Statistical Analysis Plan
Cover Page

[ASE Study]

Acute Feasibility Investigation of a New S-ICD Electrode Arrangement for Reduction of Defibrillation Energies

CLINICAL INVESTIGATION PLAN

ver. F, dated 20 Jan 2021

ClinicalTrials.gov Registration: NCT03802110

Acute Feasibility Investigation of a New S-ICD Electrode Arrangement for Reduction of Defibrillation Energies

[ASE Study]

CLINICAL INVESTIGATION PLAN

Project Number C2081

National Clinical Trial (NCT) Identified Number: NCT03802110

Eudamed Number: CIV-NL-18-11-026204

Sponsored By

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Original Release: September 5, 2017

Current Version: Nov 20th , 2019

Revision History

Revision version	Protocol Date	Template number and version	Protocol section modified	Summary of changes	Justification for Modification
A	Sept 5, 2017	90702637 Rev/Ver AH	NA	Original Release	NA
B	Mar 6, 2018	90702637 Rev/Ver AH	Section 9.3 Section 22.2	Modified Exclusion Criteria 22 to: Women of childbearing potential who are or might be pregnant at the time of the S-ICD implant procedure. Added a section for DMC	Clarified that exclusion to pregnancy is only at the time of the S-ICD implant procedure; there is no exclusion after the implant procedure. Per AMC Central EC's request.
C	May 22, 2019	90702637 Rev/Ver AL	NA	NA	Major revision to support the testing of a 2-electrode configuration (Parallel and 90º)
C	May 22, 2019	90702637 Rev/Ver AL	Contact information	Updated clinical contact	Change of CTM
C	May 22, 2019	90702637 Rev/Ver AL	Synopsis	Updated	Updated for consistency with the changes made throughout the protocol - see description of the major changes below
C	May 22, 2019	90702637 Rev/Ver AL	Section 4.2.4-Background, Figure 4-2, Table 4-1,	Added background information, figures and clarifying text to describe 2-electrode configuration (Parallel and 90º) "parallel" electrodes, described previously and a new "90º" configuration	Provide background information to justify adding testing of the 2-electrode configuration (Parallel and 90º).
C	May 22, 2019	90702637 Rev/Ver AL	8.0 – Study Design, Figure 8-1	New text and updated Figure 8-1 to describe the new 90º angle electrode configuration	Supports changes to the study procedure (see section 11.4 below)

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C	May 22, 2019	90702637 Rev/Ver AL	8.1 – Scale and Duration	Increased enrollment from 30 to 42 and complete data sets from 20 to 30.	Twenty complete data sets are needed with the new test procedure described in section 11.4. Ten data sets have already been obtained from 14 enrolled subjects. So, the enrollment and complete date set numbers were increased proportionally.
C	May 22, 2019	90702637 Rev/Ver AL	8.2 Treatment Assignment	Added description of how the order of testing will be determined based on subject enrollment #.	Testing of 2-electrode configuration (Parallel and 90º) was added so a method to determine the order of testing was needed to reduce the possibility of a test order bias.
C	May 22, 2019	90702637 Rev/Ver AL	Table 11-1	Added collection of post-operative x-rays when available as part of standard of care.	Clarification. When available, post-op x-rays may aid in the interpretation of study results.
C	May 22, 2019	90702637 Rev/Ver AL	11.4 SICD Implant Visit, Figure 11-1	Completely re-written and new Figure added. Describes the flow of the overall procedure with testing two-electrode configurations (Parallel and 90º)". The new Figure 11-1 describes a new energy test step sequence that starts at 30 J, rather than 50 J, and requires only 2 VF inductions per shock configuration.	New computer modeling data suggests two shock coils inserted at a 90° angle (an "L" configuration) might perform as well as two electrodes inserted in parallel but could result in a more favorable product. The original protocol envisioned this possibility but was not clear about how testing in another configuration should be done. So, changes to the test procedure were needed to allow testing of both configurations. This is the main reason for the protocol revision.

Revision History

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C	May 22, 2019	90702637 Rev/Ver AL	11.4.2 Temporary Insertion of the Second S-ICD Electrode	Added more specific description of how the 2nd electrode is inserted in both parallel and 90º configurations	Clarification – to support changes in 11.4 (see above)
C	May 22, 2019	90702637 Rev/Ver AL	11.4.3 Figure 11-1	Clarifications to the DFT testing procedure and stopping rules. The old Figure 11-1, originally shown in section 11.4.3 was removed and a new Figure 11-1 was added to section 11.4 (see above).	Needed to support testing of 2-electrode configuration (Parallel and 90º) per 11.4 above. Current results showed that all subjects were converting at 40 J or lower, so the starting energy was reduced to 30 J and the new testing only require 2 VF inductions per test configuration.
C	May 22, 2019	90702637 Rev/Ver AL	11.4.4 – Allowable Test Sequence Revisions	Added section 11.4.4 to describe the range, and limits, of possible changes that could be made to the test procedure.	Provide clarity about the scope and limits of changes that can be made without need for a new protocol revision.
C	May 22, 2019	90702637 Rev/Ver AL	All sections	Minor changes made throughout the document to support the major changes described above.	Consistency, clarity with the major changes
C	May 22, 2019	90702637 Rev/Ver AL	20.4 Investigator Reporting Requirements	Updated AE reporting	Updated per current Boston Scientific requirement
D	July 1 2019	90702637 Rev/Ver AL	Table 4-1. Results of computer models of defibrillation electrical fields in a realistic human torso	Peak current and peak voltage added for Two parasternal electrodes at ~90º angle	Question from CEC

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D	July 1 2019	90702637 Rev/Ver AL	20.4 Investigator Reporting Requirements	Updated AE timelines	Corrections
E	20 Nov 2019	90702637 Rev/Ver AL	11.4.1 and 11.4.3	Added Safety Criteria to Stop In-procedure Acute Testing	Updated due to unexpected system event in 2 enrolled patients.
F	20 Jan 2021	90702637 Rev/Ver AO	All	Adoption of sponsor protocol template which was modified to conform with the with the updated ISO 14155 and EU MDR Added number of Investigational devices to be used per patient Added statement that the study population is a reasonable representation of the population that would be targeted for a future SICD product Added a list of technical and functional features of the Investigational device and their related expected outcome Added the product clinical development stage Added a clarification on final database lock and storage Added a statement that the sponsor will not approve protocol waivers Added necessity for a site to enter in a	Adoption of updated ISO 14155 and EU MDR requirements

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				Clinical Study Agreement with the sponsor before commencing the trial Added that study is conducted in conformance to European Medical Device Regulation Added requirements for investigators on their qualifications and disclosure of interests Added requirement for the sponsor to have a monitoring strategy in place Clarified instances when the clinical investigation can be suspended or terminated Added obligation to register the study on a public database and to have a clinical investigation report available Added Boston Scientific data sharing policy Added definitions of source document and source data	
F	20 Jan 2021	90702637 Rev/Ver AO	Synopsis 9.3 Exclusion Criteria	Removed 2 exclusion criteria (**main driver of the protocol amendment**): Previously #7 and #8: – 7.Subject has hypertrophic cardiomyopathy.	BSC initially excluding these patients who are known to have or might have a higher defibrillation threshold. BSC and the ASE Steering Committee have agreed that it is safe to include them given the literature

Revision History

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				– 8.Subject has Brugada syndrome.	evidence and the significant potential benefit for these types of indicated patients.
F	20 Jan 2021	90702637 Rev/Ver AO	16 Device Accountability	Clarified Device Accountability requirements for both Sponsor and Investigator	Updates to the ISO 14155 standard
F	20 Jan 2021	90702637 Rev/Ver AO	20.2 Definitions and classifications	Change to the Adverse events definitions Addition of the definition of Serious Health Threat Addition of the definition of hospitalization and prolongation of hospitalization	Updates to the ISO 14155 standard
F	20 Jan 2021	90702637 Rev/Ver AO	20.3 Relationship to Study Device(s) and/or Study Procedure	Removal of one relatedness category (“unlikely related”)	Updates to the ISO 14155 standard
F	20 Jan 2021	90702637 Rev/Ver AO	22 Committees	Clarification of the role of the internal safety Monitoring Process	Updated per current Boston Scientific requirement

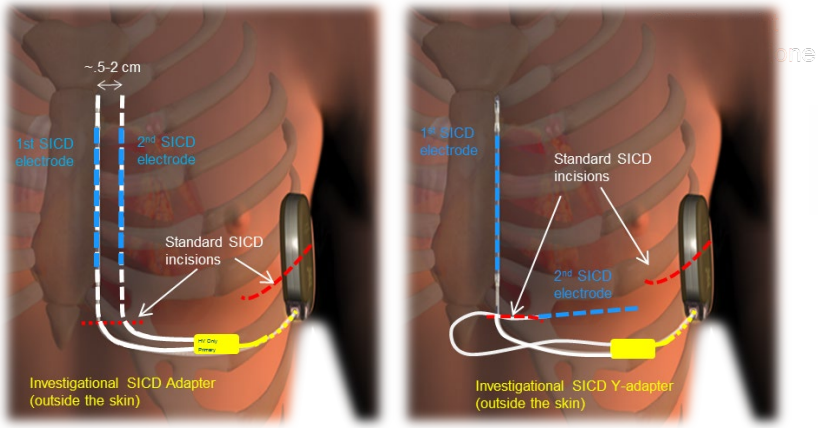
2. Protocol Synopsis

Acute Feasibility Investigation of a New S-ICD Electrode Arrangement for Reduction of Defibrillation Energies [ASE Study]	
Study Objective(s)	The primary objective of this acute feasibility study is to assess the defibrillation threshold (DFT) when adding a second left parasternal electrode to an S-ICD system. The secondary objective is to assess the efficacy of the 2-electrode configurations (Parallel and 90º) to convert VF.
Background	The current S-ICD system pulse generator (PG) is 59 cc in size and delivers a maximum energy shock of 80 J. Any significant reduction in PG size would require a reduction in the maximum energy output. Reducing the defibrillation energy requirement would increase the percentage of S-ICD subjects that could receive a smaller PG. Computer modeling of the electrical fields in a realistic human torso showed that either a wider parasternal electrode, or two parallel standard S-ICD electrodes, or two S-ICD electrodes inserted at a 90º angle, reduced shock impedance, improved current delivery and reduced defibrillation energy. Swine defibrillation studies of the subcutaneous systems with one vs. two left parasternal electrodes showed smaller and less consistent reduction in shock impedance and delivered energy than the computer models. However, swine have anatomy and electrophysiologic properties that are substantially different than humans that affect defibrillation efficiency. Thus, an acute human study with two left parasternal electrodes is necessary to determine the feasibility of improving the defibrillation efficacy using new electrode configurations.
Planned Indication(s) for Use	The Investigational S-ICD Y-Adapter is intended to facilitate ventricular fibrillation (VF) conversion testing of a novel S-ICD subcutaneous electrode configuration. The Investigational S-ICD Y-Adapter is a sterile, single-use, acute implant accessory. It is intended for short-term use during a testing procedure and must be disconnected at the end of the testing procedure.

<table>
<tr><th colspan="3">Acute Feasibility Investigation of a New S-ICD Electrode Arrangement for Reduction of Defibrillation Energies

[ASE Study]</th></tr>
<tr><td rowspan="8">Test System</td><td colspan="2">The S-ICD Defibrillation System Components and Investigational S-ICD Y-Adapter are shown in the table below:</td></tr>
<tr><td colspan="2">Commercial S-ICD System Components</td></tr>
<tr><td>Device Name</td><td>Model Number</td></tr>
<tr><td>EMBLEM S-ICD Family of Pulse Generators</td><td>A209, A219 (future models allowed when commercially released)</td></tr>
<tr><td>EMBLEM S-ICD Electrode</td><td>3401, 3501 (future models allowed when commercially released)</td></tr>
<tr><td colspan="2">Investigational Components</td></tr>
<tr><td>Device Name</td><td>Model Number</td></tr>
<tr><td>Investigational S-ICD Y-Adapter</td><td>3598</td></tr>
<tr><td colspan="2">About 1 Y-Adapter will be used per patient, unless there is a deficiency noted during the procedure. If this occurs, the Y-Adapter will be replaced by a new one. Overall, about 42 Y-Adapters will be used.</td></tr>
<tr><td>Study Design</td><td colspan="2">This is a prospective, multi-site, single-arm, acute feasibility study.</td></tr>
<tr><td>Investigational Implant Technique and Testing Methodology</td><td colspan="2">First, a commercial S-ICD system implant will be initiated via techniques used in one-electrode configuration. The first electrode is connected to the PG via the PRIMARY port of the Investigational S-ICD Y-Adapter and the S-ICD system is tested, including a standard VF induction and test shock at 65 J. The subject may proceed to additional investigational testing only if the 65 J shock converts the VF and all protocol defined safety criteria are met.

All acute testing will be completed at the index S-ICD implant procedure. For subjects proceeding to the additional investigational testing, testing in two different 2-electrode configurations (Parallel and 90º) is planned. The second S-ICD electrode will be inserted from the same incision created for the first S-ICD electrode and positioned in a separate tunnel either parallel to, or at an angle to, and more lateral to the first electrode (with a range of either 0.5-2 cm inter-electrode spacing, or 0 to 90º angles). See the 2-electrode configuration (Parallel or 90º) in the figure below. Both S-ICD electrodes are connected to the PG using the Investigational S-ICD Y-Adapter. DFT testing is then performed with the first 2-electrode configuration (Parallel or 90º) using</td></tr>
</table>

Acute Feasibility Investigation of a New S-ICD Electrode Arrangement for Reduction of Defibrillation Energies [ASE Study]	
	2 additional VF inductions and shocks per the protocol specified testing sequence. After testing is completed in the first configuration, the second configuration will be tested using 2 additional VF inductions. Lastly, after the DFT testing is completed, the second S-ICD electrode and Investigational S-ICD Y-Adapter are disconnected and removed, and the S-ICD system implant is completed per investigator's usual practice and experience. A schematic representation of the Investigational S-ICD Y-Adapter and the electrode/PG connection during investigational testing is shown below. The second electrode is either parallel to the first with 0.5-2 cm spacing (left figure) or is inserted at an ~90 degree angle from the first (right figure). 
Planned Number of Subjects	A maximum of 42 subjects will be enrolled to obtain at least 30 complete datasets.
Planned Number of Investigational Sites / Countries	A maximum of 10 sites are allowed in Europe and possibly in the United States.
Primary Safety Data	All S-ICD system and procedure related adverse events

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Primary Effectiveness Data	Defibrillation Threshold (DFT) of the 2-electrode configuration (Parallel and 90º)
Additional Data	• VF conversion success for the 2-electrode configurations (Parallel and 90º) • Shock impedance of both the one- and 2-electrode configuration (Parallel and 90º)
Method of Assigning Subjects to Treatment	All enrolled subjects are intended to have the 2nd electrode inserted and undergo acute testing. The order of 2-electrode configuration (Parallel and 90º) testing will be alternated based on the subject's ID # to help reduce the possibility of a test order bias.
Follow-up Schedule	Study procedures/visits will occur at the following time periods: • Consent and enrollment visit • S-ICD implant procedure visit • 90-day follow-up visit (to be conducted in clinic or by telephone at 90±45 days post-implant)
Study Duration	Duration of the study, from the first enrollment to the last subject's final visit is expected to be approximately 20-28 months. Individual subjects will be followed from enrollment until their 90-day follow-up visit.
Inclusion Criteria	1. Subject is scheduled to receive a de novo S-ICD system implant per labeled indication. 2. Passing S-ICD screening ECG performed per applicable user's manual. 3. Subject is expected to be implanted with a left parasternal S-ICD electrode. 4. Subject's planned S-ICD implant procedure will include at least one VF conversion testing at 65 J. 5. Subject is willing and capable of providing informed consent specific to local and national laws.

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	6. Subject is age 18 or above, or of legal age to give informed consent specific to local and national law.
Exclusion Criteria	1. Subject has an unusual chest anatomy (eg. pectus excavatum and pectus carinatum) that might impede the ability to temporarily insert a second S-ICD electrode. 2. Subject has a left ventricular ejection fraction ≤ 20% within 3 months prior to enrollment. 3. Subject has NYHA Class IV or unstable Class III heart failure. 4. Subject that, in the opinion of the investigator, cannot tolerate the DFT testing required by this protocol. 5. Subject that, in the opinion of the investigator, is at increased risk for VF conversion failure. 6. Subject is morbidly obese, defined as BMI ≥ 35. 7. Subject has an active infection or has been treated for infection within the past 30 days. 8. Subject that, in the opinion of the investigator, has an increased risk of infection. 9. Subject is currently requiring/receiving dialysis. 10. Subject has insulin-dependent diabetes. 11. Subject had/has any prior or planned other surgical procedure within ±30 days of enrollment. 12. Subject is receiving immunosupressive therapy or has a condition that compromises their immune system. 13. Subject had episodes of atrial fibrillation or atrial flutter within the 4-week period prior to enrollment or during the period of time between enrollment and the start of implant procedure. 14. Subject that, in the opinion of the investigator, has an increased risk for thromboembolic event. 15. Subject that, in the opinion of the investigator, has an increased risk of excessive bleeding. 16. Subject is currently on an active heart transplant list. 17. Subjects with documented life expectancy of less than 12 months. 18. Subject has any other electrically active implanted device that cannot be temporarily deactivated during the implant (includes

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	components or accessories present such as pulse generators, non-capped leads or leads with breached insulation, implantable cardiac monitors, implantable stimulators). 19. Subject is enrolled in a concurrent study, with the exception of local mandatory governmental registries and observational studies/registries, without prior written approval from Boston Scientific. 20. Women of childbearing potential who are or might be pregnant at the time of the S-ICD implant procedure.
Safety Criteria to Stop In-procedure Acute Testing	• The 65 J shock from the standard S-ICD system did not convert VF on the first attempt • The time from VF induction to 65 J shock delivery was >25 seconds measured from the end of the induction to the first delivered shock • The subject required more than 1 rescue shock to convert one induced VF • Hemodynamic instability per investigator's medical judgment • Excessive bleeding that requires medication, blood transfusion, or the use of blood derivatives • Any other unexpected clinical or system-related event occurs.
Statistical Methods	
Primary Statistical Hypothesis	This is an early-stage feasibility study. There is no formal hypothesis due to this study not being powered for its sample size and no control group for comparison. This study seeks to characterize the performance of new, 2-electrode configurations (Parallel and 90º) by collecting DFT test and shock impedance data.
Statistical Test Method	There are no statistical tests or comparisons. Summary statistics will be provided on DFT and VF conversion success.
Sample Size Parameters	There is no statistically computable sample size. It is anticipated that 30 complete data sets could provide a reasonable assessment of the

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	defibrillation efficacy. Up to 42 subjects will be enrolled to account for attrition.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

The Subcutaneous Implantable Cardioverter Defibrillator (S-ICD) system has been shown to be a safe and effective alternative to transvenous ICD systems and thus may be appropriate for many patients at risk for sudden cardiac death. The key advantage of the S-ICD system vs the traditional ICD system is that it is completely subcutaneous with no leads inserted in the heart chambers or vasculature. The S-ICD system therefore avoids the majority of issues associated with the transvenous ICD systems including lead dislodgement and mechanical lead failure as well as adverse events associated with the insertion of a transvenous lead. The S-ICD system is implantable using readily identifiable anatomical landmarks and thus avoids the routine need for fluoroscopy during system implant.

The current S-ICD system consists of the EMBLEM S-ICD electrode and S-ICD pulse generator. Figure 4-1 illustrates the standard locations of the electrode insertion and pulse generator (PG). The electrode is inserted subcutaneously, typically along the left sternal margin, using a subcutaneous insertion tool from a small incision in the paraxiphoid region. A commercially available peelable sheath is often used as part of the electrode insertion process. The pulse generator is placed in a subcutaneous pocket on the postero-lateral aspect of the left thorax from a lateral incision along the 5th or 6th intercostal space. The proximal end of the electrode is tunneled subcutaneously to the pulse generator pocket. The defibrillation shock is delivered between the left parasternal coil electrode and the pulse generator.

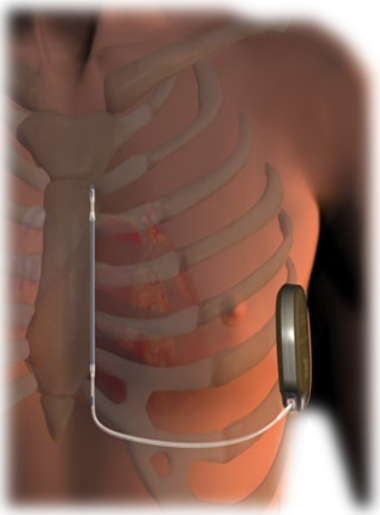

Figure 4-1. Commercially available S-ICD system shown in the typical implanted locations.

While the S-ICD system has gained considerable commercial adoption as an alternative to transvenous ICD systems, a factor limiting its more widespread usage is the size of the S-ICD pulse generator. The first commercially available S-ICD pulse generator introduced by Cameron Health (model 1010) was 69 cc. After acquisition of Cameron Health, Boston Scientific employed technological enhancements to key components that allowed for a size reduction to 59 cc. However, commercially available transvenous ICD pulse generators are still significantly smaller, in the range of ~30-35 cc. The most important factor contributing to the larger size of the S-ICD is the significantly higher energy output required in the S-ICD. The S-ICD delivers an 80 J shock, while the transvenous ICD systems typically deliver ~35-40 J.

Technology advances will likely allow additional reduction in S-ICD size. Engineering assessment suggests that a pulse generator near 50 cc in size might be possible. A more substantial reduction in pulse generator size can only be accomplished by reducing the energy output of the S-ICD. Energy output of the S-ICD pulse generator can only be reduced if the energy required to successfully convert ventricular fibrillation (VF) is low enough while ensuring an appropriate safety margin.

Therefore, the primary objective of this study is to investigate a new parasternal electrode configuration that uses a second parasternal electrode to reduce shock impedance and reduce defibrillation energy requirements. If results are favorable, Boston Scientific could use the information to design a new parasternal electrode and a new, smaller, lower energy pulse generator. The study will enroll patients already scheduled for an S-ICD implant and therefore the investigational population should be a reasonable representation of the population that would be targeted for a future SICD product.

4.1. *Background*

Transvenous ICD and S-ICD systems have traditionally used acute VF conversion testing at the time of system implantation to demonstrate successful VF conversion at an energy level lower than the maximum energy of the pulse generator to allow for a safety margin. ICD safety margins have typically been set ~10 J. In the US S-ICD Pre-market Clinical Study (*G090013*, commenced 11Dec09), a 15 J safety margin was tested. Thus, acute VF conversion efficacy at 65 J is typically tested during an S-ICD implant. If patients could be converted at energies lower than 65 J, they could potentially receive a smaller, lower energy S-ICD pulse generator. Engineering analysis suggests that a 60 J S-ICD pulse generator could be close to 40 cc in size, which is a substantial reduction compared to 59 cc in an 80 J device.

Data collected from an early S-ICD study of 49 subjects showed that the S-ICD system had mean DFT of ~37±20 J, and that 38 out of 49 subjects had at least one successful conversion at 50 J or lower[1]. Data from two other studies showed the S-ICD system converted VF at energies less than or equal to 50 J in 12 out of 16 subjects with hypertrophic cardiomyopathy [2] and 11 out of 15 subjects in a subset of the US S-ICD Post-Approval Study (*P110042*, commenced 28Sep12 as conditions of approval). Thus, while small in number,

the available data suggest that between 70% and 80% of current S-ICD recipients might already meet defibrillation requirements to allow the use of a 60 J pulse generator. Improvements to the S-ICD electrode system that reduced defibrillation energy requirements would increase the percentage of subjects able to receive a smaller, lower energy S-ICD system.

4.2. *Bench Test, Computer Modeling, and Pre-clinical Study Results*

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s

4.2.2. Pre-Clinical Testing of an Alternative S-ICD Electrode System

[redacted]

[redacted]

[redacted]

4.3. *Safety of Acute VF Conversion Testing*

4.3.1. ICD Experience

The implantation of ICD and S-ICD systems has a long history of performing VF conversion testing at the time of system implant. The rationale for such testing is threefold: 1) to ensure appropriate sensing and detection of VF, 2) to obtain evidence of successful VF conversion of the system and, 3) to help ensure a safety margin exists between an energy level known to convert VF and the maximum output of the device.

Available data suggests that VF conversion testing and evaluation of the DFT is safe when conducted by experienced implanters with the right training and backup defibrillation support. There are many published studies that evaluated paired DFT of new shock electrodes[6-8], different shock vectors[9-11], and different shock waveforms[12-25]. Such testing would typically require 3 to 5 VF inductions and shocks per test configuration to assess the DFT of each test configuration. One large trial of DFT testing was the Low Energy Safety Study (LESS)[26], sponsored by Boston Scientific Corporation . Seven hundred and thirty-three (733) subjects underwent extensive VF conversion testing at implant, and a subset of 392 subjects had additional VF conversion testing at pre-discharge, 3 months, and 12 months. Implant testing consisted of the determination the DFT (in which the lowest energy level that succeeds was reconfirmed twice, for a total of 3 tests without failure). This testing typically required 4 to ~14 VF inductions and shocks delivered per subject. Follow-up testing in the Phase 1 subset of 392 subjects consisted of 3 VF inductions and shocks at each of the three follow-up visits, for a total of 9 additional VF conversion tests. Testing was generally well tolerated.

While VF conversion testing is generally well tolerated, some physicians began questioning whether it was routinely necessary. The landmark SIMPLE Study, funded by Boston Scientific Corporation , randomized 2500 subjects receiving their first ICD or CRT-D system to implantation with or without VF conversion testing[27]. After a median follow-up of 3.1 years outcomes including total mortality and failed appropriate shocks or arrhythmic death were similar. All planned non-inferiority tests showed no disadvantage of the strategy of implanting without a VF conversion test. While this study is most often cited to support the practice of implantation of an ICD without VF conversion test, the data also shows that VF conversion testing was well tolerated. There were no deaths attributable to VF conversion testing and there was no difference in the safety composite between subjects with VF conversion test at implant versus those without. Retrospective and underpowered sub-analysis suggested a slight increase in the need for temporary chest compressions (0.4%) and non-elective intubation (0.6%) in the group with VF conversion tests; however, unplanned stay in the Intensive Care Unit (ICU) was slightly higher in the group without VF conversion tests (0.3%).

While the results of SIMPLE Study have led most transvenous ICD implanters to stop routine VF conversion testing at implant and medical society consensus statement suggests that it is reasonable to omit VF conversion testing in ICD implant under specified conditions

[28], it's important to note that Boston Scientific's instructions for use of ICD products still suggest VF conversion testing. Thus, while the practice of ICD implantation is changing it should not be inferred that VF conversion testing is unsafe.

4.3.2. S-ICD Experience

S-ICDs are a new addition to the range of devices available to protect subjects at risk for sudden cardiac death. Because of the differences in implant location, implant technique and the lower level of experience physicians have with S-ICD implantation, VF conversion testing at implant is recommended and still routinely performed. The 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing recommends defibrillation efficacy testing in subjects undergoing an S-ICD implantation[28]. Boston Scientific's instructions for use of S-ICD system also recommend VF conversion testing at S-ICD implant. All major trials of S-ICD have suggested that VF conversion testing be performed. In the US S-ICD Pre-market Clinical Study (*G090013*)[29], the protocol required physician investigators to demonstrate two consecutive successful VF conversions at 65 J. To accomplish this, the protocol required up to 8 total VF conversion tests. In this study subjects received an average of 2.56 VF inductions and shocks (range: 2 to 8). The overall VF conversion success rate in the study was 98.4%.

In the initial stages of S-ICD exploration, prior to commercialization, several acute clinical studies were performed using fairly extensive DFT testing to investigate the use of various electrodes designs, shock configurations and shock waveforms[1]. No serious adverse events were reported.

Thus, the totality of experience with S-ICD suggests that VF conversion testing, including multiple VF inductions and DFT testing, can be safely performed.

4.3.3. Summary of Clinical Experience

The available data, as described above, shows that VF conversion testing in both ICD and S-ICD recipients has been a widely performed and generally accepted practice that is well tolerated in the vast majority of subjects. While adverse events related to VF induction testing may occur, they are rare. One commonly reported adverse events related to VF induction testing is slow hemodynamic recovery following VF conversion[27], and it can be effectively managed with little long-term consequence to the subject.

Based on these clinical experiences, a set of safety principles for conducting VF conversion tests acutely in humans is applied to the design of this study. These include: 1) subject will only proceed to two-electrode VF conversion test if VF conversion at 65 J using one-electrode is successful; 2) subjects who are hemodynamically unstable or unable to tolerate VF conversion test, and those with increased risk of infection and excessive bleeding are excluded from study participation; 3) backup defibrillation equipment is required; 4) Pre-

specified criteria for Boston Scientific Medical Safety to initiate safety event review are established for certain serious adverse events occurring at a frequency greater than expected (See Section 11.4.6 and 11.5.1).

5. Device Description

The acute testing performed in this study utilizes commercially released S-ICD system and accessories, and the Investigational S-ICD Y-Adapter.

5.1. Commercially Available Components:

Device Category	Device Name	Model Number
Pulse Generators	EMBLEM S-ICD Family of Pulse Generators	A209, A219
Electrode	EMBLEM S-ICD Electrode	3401, 3501
Accessories	Electrode Introducer tool (EIT) kit	4711
	11 French introducer sheaths	7097 (15 cm), 7131 (25 cm)
Non-Implanted Components	S-ICD PRM	3200
	Torque wrench	6628

Future product models will be allowed when market approved and commercially released.

5.2. Investigational S-ICD Y-Adapter

The Investigational S-ICD Y-Adapter (model 3598) is intended to facilitate ventricular fibrillation (VF) conversion testing of a novel S-ICD subcutaneous electrode configuration.

The Investigational S-ICD Y-Adapter is a sterile, single-use, acute implant accessory. It is intended for short-term use during a testing procedure and must be disconnected at the end of the testing procedure.

For the purpose of the investigational testing for this study, the S-ICD Y-Adapter connects two S-ICD subcutaneous electrodes to an S-ICD pulse generator. It consists of a long tail with an SQ-1 connector pin and a header with two SQ-1 connector ports.

[redacted]

[redacted]

[redacted]

5.3. *Required* Medical Equipment

While not specifically part of the study system provided by Boston Scientific, additional equipment provided by the investigational center required for the study include:

- Back-up external defibrillator for emergency rescue
- Continuous blood pressure monitoring
- Fluoroscopic imaging equipment

6. Study Objectives

The primary objective of this acute feasibility study is to assess the defibrillation threshold (DFT) when adding a second left parasternal electrode to an S-ICD system 2-electrode configuration

The secondary objective is to assess the efficacy of 2-electrode configurations (Parallel and 90º) to convert VFJ.

The tertiary objective is to assess factors that influence the DFT when adding the second electrode (e.g. spacing and orientation or angle between electrodes).

7. Study Data

Primary Data:

- All device- and procedure-related adverse events
- The DFTs for the 2-electrode configuration (Parallel and 90º) consisting of two left-parasternal electrodes to left lateral PG

Secondary Data:

- The shock impedance for each of the two S-ICD shock configurations (one parasternal electrode and two parasternal electrodes)
- VF conversion success for the 2-electrode configuration (Parallel and 90º)

8. Study Design

The clinical development stage of the 2-electrode configuration S-ICD system is a pilot stage (per ISO 14155, annex I). As such, the study has an exploratory design with no pre-specified hypotheses and implies an interventional burden on the study subjects (e;g; additional testing at implant that is not standard of care).

This study is a multicenter, single-arm, early feasibility assessment of new S-ICD shock configurations (See Figure 8-1) that consist of two S-ICD electrodes inserted from the left-parasternal region.

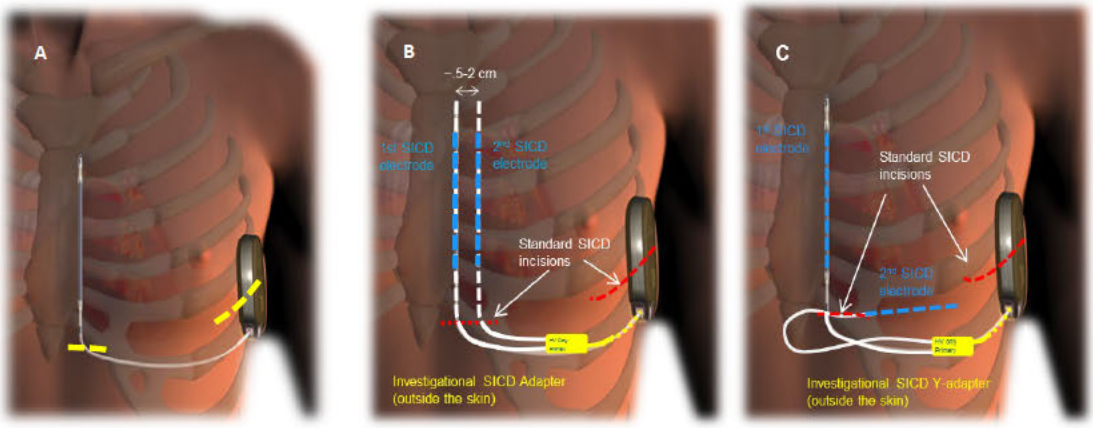

Figure 8-1. The shock configurations to be used in this study.

A) standard S-ICD shock vector consisting of left parasternal electrode to postero-lateral pulse generator. B) alternative S-ICD shock vector consisting of two parallel left parasternal electrodes inserted 1-2 cm apart to a postero-lateral pulse generator, C) alternative S-ICD shock vector consisting of two electrodes inserted at ~90° angle to a postero-lateral pulse generator

8.1. *Scale and Duration*

This study will enroll up to 42 subjects to achieve a complete data set in 30. Complete dataset is defined as those subjects who completed the entire VF conversion testing procedure as specified in Section 11.4. Since some subjects may exit the study before the procedure begins and since repeated VF conversion tests to determine the DFT may not be possible in every subject for a variety of reasons that are not predictable prior to enrollment, the study allows for adequate enrollment to help ensure a meaningfully evaluable dataset.

The study will be conducted at approximately 3-5 centers, and a maximum of 10 sites are allowed in Europe and possibly in the United States. Study enrollment is expected to take 20-28 months.

8.2. *Treatment Assignment*

This is an acute study performed during a routine S-ICD implant. All enrolled subjects are intended to have the 2nd electrode inserted and undergo acute testing. The order of 2-electrode configuration testing will alternate based on the subject's study ID number to help reduce the possibility of a test order bias. If the subject ID number is odd (e.g. AS-1111-03) then start with the parallel configuration, if the subject ID number is even (e.g. AS-1111-04) then start with the 90° configuration.

8.3. *Justification for the Study Design*

This is an early feasibility study designed to assess the performance of a second parasternal electrode as part of an S-ICD system. Computer modeling and VF conversion testing in swine have already been done (see Section 4.2). All data suggests the use of either a second coil electrode or a single "wider" electrode can reduce both the shock impedance and the energy required for defibrillation. However, only clinical testing can determine the actual performance in shock impedance and energy requirements in humans. This study will determine if a new electrode configuration will decrease energy requirement that would enable a reduction in the size of the S-ICD pulse generator. Size reduction would have a significant benefit to future S-ICD recipients.

9. Subject Selection

9.1. *Study Population and Eligibility*

Subjects will be identified by the physician investigator from the general population of subjects being implanted with a new S-ICD system.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

Table 9-1: Inclusion Criteria

Inclusion Criteria	1. Subject is scheduled to receive a de novo S-ICD system implant per labeled indication. 2. Passing S-ICD screening ECG performed per applicable user's manual. 3. Subject is expected to be implanted with a left parasternal S-ICD electrode. 4. Subject's planned S-ICD implant procedure will include at least one VF conversion testing at 65 J. 5. Subject is willing and capable of providing informed consent specific to local and national laws. 6. Subject is age 18 or above, or of legal age to give informed consent specific to local and national law.

Abbreviations: VF : ventricular fibrillation

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9-2) will be excluded from this clinical study.

Table 9-2: Exclusion Criteria

Exclusion Criteria	1. Subject has an unusual chest anatomy (eg. pectus excavatum and pectus carinatum) that might impede the ability to temporarily insert a second S-ICD electrode. 2. Subject has a left ventricular ejection fraction ≤ 20% within 3 months prior to enrollment. 3. Subject has NYHA Class IV or unstable Class III heart failure. 4. Subject that, in the opinion of the investigator, cannot tolerate the DFT testing required by this protocol. 5. Subject that, in the opinion of the investigator, is at increased risk for VF conversion failure. 6. Subject is morbidly obese, defined as BMI ≥ 35. 7. Subject has an active infection or has been treated for infection within the past 30 days. 8. Subject that, in the opinion of the investigator, has an increased risk of infection. 9. Subject is currently requiring/receiving dialysis. 10. Subject has insulin-dependent diabetes. 11. Subject had/has any prior or planned other surgical procedure within ±30 days of enrollment. 12. Subject is receiving immunosupressive therapy or has a condition that compromises their immune system. 13. Subject had episodes of atrial fibrillation or atrial flutter within the 4-week period prior to enrollment or during the period of time between enrollment and the start of implant procedure. 14. Subject that, in the opinion of the investigator, has an increased risk for thromboembolic event. 15. Subject that, in the opinion of the investigator, has an increased risk of excessive bleeding. 16. Subject is currently on an active heart transplant list. 17. Subjects with documented life expectancy of less than 12 months. 18. Subject has any other electrically active implanted device that cannot be temporarily deactivated during the implant (includes components or accessories present such as pulse generators, non-capped leads or leads with breached insulation, implantable cardiac monitors, implantable stimulators). 19. Subject is enrolled in a concurrent study, with the exception of local mandatory governmental registries and observational studies/registries, without prior written approval from Boston Scientific. 20. Women of childbearing potential who are or might be pregnant at the time of the S-ICD implant procedure.

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects meeting all the inclusion criteria and not meeting any of the exclusion criteria may be approached for enrollment. Subjects will be considered enrolled at the point they sign the informed consent form. All subjects signing the informed consent form and having acute testing attempt (reached Attempt Classification, see Section 10.3) will count towards the enrollment ceiling.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the 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.

10.3. *Subject Status and Classification*

The status of study subjects will be classified as follows:

Enrolled: a subject who has signed and dated the informed consent form

Intent: a subject who signs the informed consent form but does not initiate any part of the S-ICD implant procedure. These include subjects who were found ineligible after consent but prior to S-ICD implant. A withdrawal form will be submitted and the subject is exited from the study and will not be counted towards enrollment ceiling.

Attempt: a subject who has any part of the S-ICD implant procedure started.

Partial Treatment: a subject who has the Investigational S-ICD Y-Adapter connected to the S-ICD pulse generator and the first electrode.

Treatment: a subject who initiates the investigational testing in the 2-electrode configuration (Parallel and 90º) Enrollment Controls

Study sites will be allowed to enroll until the enrollment ceiling of 42 subjects.

10.4. *End-of-Study Action Plan*

The Investigational S-ICD Y-Adapter and the second S-ICD electrode are temporarily used during the testing procedure and will be returned to Boston Scientific. Upon completion of the implant procedure the subjects will have a commercial S-ICD system implanted. The study will end when the last subject who has either attempted or completed the acute study procedure has completed the 90-day follow-up phone call or visit. Upon completion of the study, subjects will be followed per standard of care.

11. Study Methods

11.1. *Data Collection*

Data are collected at the following time points specified in Table 11-1. Reportable adverse events and device deficiencies are reported on an ongoing basis and throughout a subject's participation of the trial.

Table 11-1: Data Collection Schedule

Procedure/Assessment	Enrollment Visit	S-ICD Implant Procedure Visit (within 30 days after Enrollment)	90-day Follow-up Visit (90±45 days Post-implant)
Informed consent form, including informed consent signature and date	X		
Demographics, including date of birth, gender, and race and ethnicity	X		
Physical assessment, including weight and height	X		
Medical history and current medication	X		
S-ICD System information and implant data collection		X	
65 J VF conversion test (one-electrode configuration) data collection		X	
Acute DFT Testing (2-electrode configuration (Parallel and 90º) data collection, including: • Temporary insertion of the second electrode and documentation of electrode locations with fluoroscopy (saved images)		X X	
Transfer of S-ICD firmware and programmer log files		X	

Table 11-1: Data Collection Schedule

Procedure/Assessment	Enrollment Visit	S-ICD Implant Procedure Visit (within 30 days after Enrollment)	90-day Follow-up Visit (90±45 days Post-implant)
Post-operative x-rays, if standard of care		X	
Adverse events/device deficiencies*	Collected throughout the trial starting from the time of the subject's enrollment		

X = required
*See Section 20.1 for a summary of reportable adverse events in the study.

11.2. *Study Candidate Screening*

There is no formal screening process for this study and no screening logs will be required.

11.3. *Informed Consent/Enrollment Visit*

Subjects who sign and date the informed consent form are considered enrolled in the study. Consent/enrollment may take place prior to or on the same day of the S-ICD system implant but must occur within 30 days prior to the implant procedure. Subject informed consent will be obtained prior to any data collection or study procedures.

Subject's demographics, baseline medical history, current medication, and physical assessment will be obtained at the enrollment visit.

11.4. *S-ICD Implant Visit*

The overall flow of the ASE study testing, after the initial S-ICD implant, will follow Figure 11-1. Overall flow of the S-ICD implant and ASE study testing. First, the S-ICD system implant will be started per standard of care. The electrode will be connected to the PG with the Investigational S-ICD Y-Adapter and the single coil configuration tested at 65 J. If the S-ICD system successfully converts VF with 65 J and the safety criteria described in section 11.4.1 are met, the additional investigational testing will proceed. There are two different 2-electrode configurations (Parallel and 90º) that will be tested. The order of testing of 2-electrode configuration (Parallel and 90º) will alternate based on the subject's ID number to help reduce the possibility of a test order bias. Each subject follows only one path in the flow chart of Figure 11-1.

Section 11.4.2 describes how the 2nd electrode is inserted for the parallel and 90º configurations.

Section 11.4.3 describes the how the VF conversion testing is performed. It is expected that testing of each 2-electrode configuration (Parallel and 90°) will require 2 VF inductions and will use the energy test step sequence shown in Figure 11-1. After the first 2-electrode configuration is tested, the 2nd electrode is repositioned, and the VF conversion testing is repeated. Subjects must meet the safety criteria described in 11.4.3 to continue with testing. If any of the safety criteria are not met, the testing will stop. When the additional investigational testing is either completed, or stopped, the 2nd electrode and Investigational S-ICD Y-Adapter will be removed and the S-ICD implant completed per standard of care.

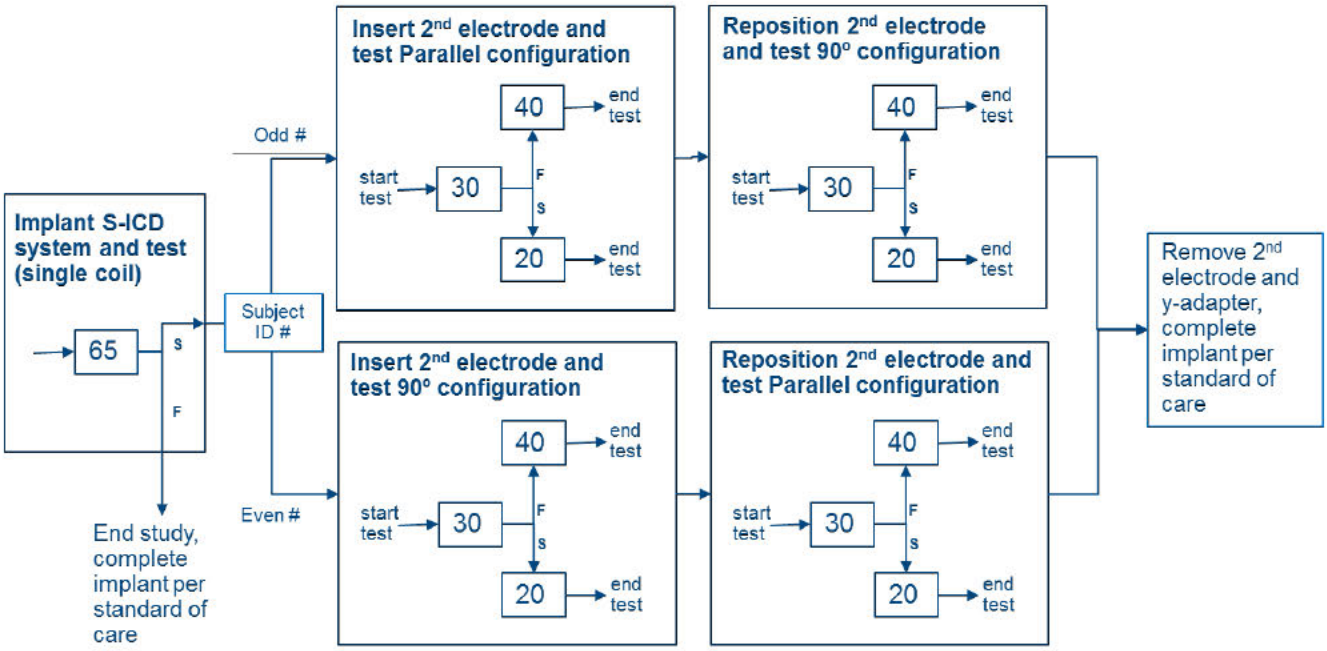

Figure 11-1. Overall flow of the S-ICD implant and ASE study testing

11.4.1. S-ICD Implant and Initial Testing

The S-ICD should be implanted according to the system's labeling. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

20. *Using shipping labels provided, return both the used second electrode and the used Investigational S-ICD Y-Adapter to Boston Scientific Product Return department for analysis.

[redacted]

[redacted]

11.4.6. Adverse Event Notification during Acute Clinical Testing in the S-ICD Implant Procedure Visit

If the following adverse events occur during the S-ICD implant and acute testing procedure, they shall be communicated within 24 hours to Boston Scientific clinical study team:

- subject death
- excessive bleeding that requires medication, transfusion, or the use of blood derivatives
- unplanned hemodynamic/cardiovascular support

Boston Scientific Medical Safety will conduct a safety review and may request additional event information to facilitate its review. Boston Scientific shall communicate to all investigators if subject enrollment and implant procedures shall be postponed pending further safety review and will communicate to all investigators when enrollment and implant procedures could resume after the safety review is completed.

11.5. *90-Day Follow-up Visit*

11.5.1. Adverse Event Notification On or Prior to the 90-day Follow-up Visit

Ninety days (with ±45 days visit window allowed) after the S-ICD implant and test procedure the subject will either visit the investigator's clinic or be contacted by phone from the investigator or delegated staff to check on their health status. A chart review will also be performed.

If the following adverse events occur on or prior to the subject's 90-day follow-up visit, they shall be communicated within 24 hours of awareness to Boston Scientific clinical study team:

- subject death
- S-ICD system infection
- excessive bleeding that requires medication, transfusion, or the use of blood derivatives
- unplanned hemodynamic/cardiovascular support

Boston Scientific Medical Safety will conduct a safety review and may request additional event information to facilitate its review. Boston Scientific shall communicate to all investigators if subject enrollment and implant procedures shall be postponed pending further safety review and will communicate to all investigators when enrollment and implant procedures could resume after the safety review is completed.

Any study reportable adverse events that have not been reported previously will be submitted on the Adverse Event case report form (CRF). See Section 20.1 for a summary of all reportable adverse events in the study.

11.6. *Study Completion*

A subject's participation in the study will end after completion of the 90-day follow-up visit. After completion in the study, subjects will be followed per standard of care.

11.7. *Source Documents*

Participating investigators must maintain original source documents that are accurate, complete, and current related to the subject's participation in this study. Source documentation must include but is not limited to those listed in Table 11-2:

Table 11-2: Source Documentation Requirements

Requirement	Disposition
• Signed informed consent forms for each enrolled subject • S-ICD pre-implant screening report • Demographics, medical history and medication use per center's subject records (EMR, etc.) • Physical assessment including height and weight • Acute procedure data Technical Source Form • Adverse events and device deficiencies • If VF conversion test was performed: Induced VT/VF episode and Induction Report for all episodes shocked • Programmer Printouts: - Final Summary Report - Device Episode Report(s), if applicable • Reportable Adverse Events, Device Deficiencies, and Protocol Deviations if applicable	Retain at site
• Fluoroscopic images or X-rays, if taken in-procedure, or post-operatively, to	Retain at site and send a copy to Boston Scientific

Table 11-2: Source Documentation Requirements

Requirement	Disposition
confirm the electrode and pulse generator locations	
• Save S-ICD programmer log files to SD card at the completion of the acute testing	Retain SD card at site and transfer data electronically to BSC via LATITUDE Link or Camelion Server

12. Statistical Considerations

12.1. *Study Data*

12.1.1. Primary Data and Secondary Data

Primary Data

1. Safety: All device- and procedure-related adverse events through 90 days post-implant procedure.
2. Effectiveness: defibrillation threshold (DFT) of the two-electrode shock configuration - two left-parasternal electrodes to the left lateral PG.

Secondary Data

1. Shock impedance of the electrode conversion tests using both the single electrode (at 65 J) and the 2-electrode configurations (Parallel and 90º).
2. Percentage of defibrillation success of VF conversion at each of the tested energy level

Hypotheses

This is an early-stage feasibility study. There is no formal hypothesis due to study not being powered for its sample size and no control group for comparison. This study seeks to characterize the performance of the new electrode shock configuration by collecting defibrillation conversion and shock impedance data.

Sample Size

This is an early-stage feasibility study and there is no formal sample size calculation. It is estimated that 20 subjects with complete testing, within an electrode configuration, will allow for a reasonable confidence in assessing defibrillation performance. For example, if 19 out of 20 subjects are successfully converted at 50 J (95% success) the resulting 95% confidence interval will be 75.13% to 99.87% using exact test, which is considered acceptable for this early feasibility assessment.

Since some enrolled subjects may not start and/or complete testing due to a variety of reasons, including exceeding the protocol-required safety criteria per Sections 11.4.2 and 11.4.3, and since a protocol revisions was made to add testing of a 2nd 2-electrode configuration (90º configuration), the study will enroll up to 42 subjects so that 30 complete datasets can be expected.

Statistical Methods

This is an early-stage feasibility study to assess performance of the new electrode shock configurations. No specific statistical tests will be performed. Descriptive statistics will be provided as follows,

- Subject demographic and medical history data will be reported as raw numbers and percentage for categorical variables and mean ± standard deviation for continuous variables.
- DFTs and shock impedances will be reported as mean ± standard deviation.
- Defibrillation success at a given energy level (eg 50 J, etc.) will be reported as a percentage and 95% confidence interval.
- System and procedure related adverse events occurrence and percentage will be collected and reported starting from the time of the subject enrollment.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

Primary Safety analyses will include all Attempt, Partial Treatment, and Treatment subjects, as defined in Section 10.3.

Primary Effectiveness analyses will include all Treatment subjects.

Secondary Effectiveness analyses of one-electrode shock data will include both Partial Treatment and Treatment subjects. Secondary Effectiveness analyses of 2-electrode configuration (Parallel and 90º) shock data will include Treatment subjects.

12.2.2. Number of Subjects per Investigative Site

It is expected that 42 subjects will be enrolled in up to 10 investigative sites.

12.3. *Data Analyses*

12.3.1. Interim Analyses

Boston Scientific will monitor the data and perform ongoing analyses on test procedures, and to identify possible safety or futility concerns. For a small early-stage feasibility study such interim analysis cannot be statistically planned or derived. However, the following effectiveness futility triggers are being established and a test configuration may be dropped, or the study will end if these criteria are met.

- <10% reduction in mean shock impedance (after a minimum of 10 subjects enrolled)
- >3 subjects that fail conversion success with 40 J shocks (4 subjects need to fail)

12.3.2. Changes to Planned Analyses

Changes from the planned statistical methods outlined in this protocol will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded on the Technical Source Forms (TSF) and paper case report forms (CRFs) provided by Boston Scientific, and on source documentation. The CRF data shall be derived from and consistent with the source documents and TSFs. Any discrepancies must be explained in writing. Per Good Clinical Practice (GCP), any change or correction made to the original clinical data will be initialed, dated, and explained, if necessary, and shall not obscure the original entry. A written audit trail shall be maintained which will be made available for review by Boston Scientific.

The TSFs are intended to be used to document procedure data during the S-ICD implant where source documentation is not available, and are to be completed by trained, qualified and investigator-authorized staff or Boston Scientific representative. The investigator and the Boston Scientific representative (if present to document the procedure data) will both sign the TSFs to confirm that the forms are a true source of procedure data.

The Principal Investigator will provide their signature on the appropriate source documents, TSFs, and CRFs in compliance with local regulations. A copy of the paper CRFs must be submitted to Boston Scientific. Changes to data previously submitted to the sponsor require a new signature by the Investigator or his/her designee to acknowledge and approve the changes.

Visual review of source documents, TSFs, and CRFs will be performed to identify possible data discrepancies. Manual queries will be created and issued to the site for appropriate response. Site staff will be responsible for resolving all queries.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities will be completed.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP (International Conference on Harmonization/Good Clinical Practice) guidelines. Documents must be retained until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product or until they are no longer needed to support regulatory applications by the study sponsor. These documents will be retained for a longer period of time by agreement with Boston Scientific or in compliance with other country/regional/local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and Boston Scientific must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

14. Amendments

If there are any changes to the study that affect the rights, safety or welfare of the subject or the scientific integrity of the data, an amendment to this Clinical Investigation Plan is required. Appropriate approvals (e.g., EC/CA) of the revised Clinical Investigation Plan must be obtained prior to implementation.

15. 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 EC , and the regulatory authority, if applicable 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 paper CRF. Sites may also be required to report deviations to the EC and the regulatory authority, per national guidelines and government regulations.

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

The sponsor will not approve protocol waivers.

16. Device/Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. The investigational device inventory log will be used to track device usage during the study. The Investigational S-ICD Y-Adapter is considered an investigational device in this study.

For the Y-Adapters labelled as investigational, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable).
- Return used Y-Adapters after use and return unused or expired Y-Adapters at the end of the study or upon Sponsor request. .

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

Records shall be kept by the Principal Investigator or his/her designee to document the physical location and conditions of storage of all investigational devices.

- Maintain records of the physical location and conditions of storage of items labelled as investigational.

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

- Maintain accurate and timely Device Accountability Records, providing copies to Sponsor upon request. Such records shall include the following content, at minimum:
  - Name of person who received, used, returned or disposed of each item
  - Date of receipt
  - Identification and quantity of each item (examples of identification: batch number, serial number or unique code)
  - Expiry date for each item (or batch of items), as applicable
  - Date or dates of use
  - Subject identification
  - Date on which the item was returned /explanted from subject, if applicable
  - Date of return (and number) of unused, expired, no longer needed or malfunctioning item, as applicable

Date and documentation of item disposal, as directed by sponsor, if applicable.

Written procedures may be required by national regulations.

The sponsor may provide commercially approved devices upon logistics and preferences of the individual study sites. All shipment, disposition and return of such devices should be tracked and unused devices should be returned to the sponsor.

17. Compliance

17.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with the European Medical Device Regulation, ISO14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and regulatory authority has been obtained. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate. An Investigator Brochure is created to support the study.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing 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 Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page 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 site 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 as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE, if required by the national regulations or this protocol or by the EC, and supply Boston Scientific 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 is used only by authorized/designated users and in accordance with this protocol and instructions for use.

- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local 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 Informed Consent Form (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.
- 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.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal 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.

17.3. *Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their Ethics Committee (EC) is registered or that registration has been submitted to the appropriate agency, if applicable according to national/regulatory requirements.

A copy of the written EC and competent authority (CA) 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. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

17.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific concerning subjects or their participation in this study will be considered confidential by Boston Scientific. Only authorized Boston Scientific personnel or a Boston Scientific representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by Boston Scientific 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' identifiable 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.

17.4.1. 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 Boston Scientific equipment/devices (including the Investigational S-ICD Y-Adapter, PG and electrodes, programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, Boston Scientific 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.

- Provide instructions for the safe return of investigational products. For potentially hazardous items, provide specialized instructions and materials, as applicable.
- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Assisting in performing PG and lead testing using a programmer to obtain DFT, lead sensing, 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 investigational S-ICD system, the programmers and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during the implant procedure and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, Boston Scientific 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 investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data on paper case report forms

17.5. *Insurance*

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

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research 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 Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by Boston Scientific personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

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

19. Potential Risks and Benefits

19.1. *Anticipated Adverse Events*

Potential adverse events related to implantation of the S-ICD System may include, but are not limited to, the following risks listed in Table 19-1. There may also be additional risks which are unknown at this time.

Table 19-1. Potential Adverse Events for Implantation of the S-ICD System

Acceleration/induction of atrial or ventricular arrhythmia	Inability to defibrillate or pace
Adverse reaction to induction testing	Inappropriate post shock pacing
Allergic/adverse reaction to system or medication	Inappropriate shock delivery

Table 19-1. Potential Adverse Events for Implantation of the S-ICD System	
Bleeding	Infection
Conductor fracture	Injury to or pain in upper extremity, including clavicle, shoulder, and arm
Cyst formation	Keloid formation
Death	Migration or dislodgement
Delayed therapy delivery	Muscle/nerve stimulation
Discomfort or prolonged healing of incision	Nerve damage
Electrode deformation and/or breakage	Pneumothorax
Electrode insulation failure	Post-shock/post-pace discomfort
Erosion/extrusion	Premature battery depletion
Failure to deliver therapy	Random component failures
Fever	Stroke
Hematoma/seroma	Subcutaneous emphysema
Hemothorax	Surgical revision or replacement of the system
Improper electrode connection to the device	Syncope
Inability to communicate with the device	Tissue redness, irritation, numbness or necrosis
*Note: If any adverse events occur, invasive corrective action and/or S-ICD system modification or removal may be required. Subjects who receive an S-ICD system may develop psychological disorders that include, but are not limited to, the following: • Depression/anxiety • Fear of device malfunction • Fear of shocks • Phantom shocks	

19.2. *Incremental Risks Associated with the ASE Study Participation*

The investigational aspects of the ASE study may increase the some of the risks listed in Table 19-1. These may include but not limited to those listed in Table 19-2. There may also be additional risks which are unknown at this time as to be related to the participation of the ASE study.

Table 19-2. Potential Incremental Risks Related to the Participation of the ASE Study
Adverse reaction to induction testing
Bleeding
Death
Discomfort or prolonged healing of incision
Electrode deformation and/or breakage
Failure to deliver therapy
Hematoma/Seroma
Improper electrode connection to the device
Inability to defibrillate or pace
Inappropriate post shock pacing
Inappropriate shock delivery
Infection
Injury to or pain in upper extremity, including clavicle, shoulder, and arm
Nerve damage
Post-shock/post-pace discomfort
Premature battery depletion
Tissue redness, irritation, numbness or necrosis
Note: If any adverse events occur, invasive corrective action and/or S-ICD system modification or removal may be required.

19.3. *Incremental Risks Associated with the Investigational S-ICD Y-Adapter*

The Investigational S-ICD Y-Adapter used in this study may increase some of the risks listed in Table 19-1. These may include but not limited to those listed in Table 19-3. There may also be additional risks which are unknown at this time as to be related to the use of the Investigational S-ICD Y-Adapter.

Table 19-3. Potential Incremental Risks Related to the Investigational S-ICD Y-Adapter
Electrode deformation and/or breakage
Inability to defibrillate or pace
Improper electrode connection to the device
Poor electrical connections
Random component failure

19.4. *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 Boston Scientific with all pertinent information required by this protocol.

19.5. *Anticipated Benefits*

Individual subjects may not receive direct benefit from participation in this study.

The study may have a significant benefit to future S-ICD recipients if the results of this study are favorable and allow the development of new S-ICD systems that reduce defibrillation energies with significantly smaller pulse generators. Thus, a subject participating in this study may receive an indirect benefit at a later date – for example at the time of pulse generator replacement.

19.6. *Risk to Benefit Rationale*

While the risks of VF conversion testing are not zero, the risks in a carefully controlled clinical trial with experienced investigators are very low. Many such studies have been performed previously that led to many important developments in ICD and S-ICD therapy that have benefited hundreds of thousands of recipients. Improvements to S-ICD therapy simply cannot be made without studies of this type.

The risk to benefit ratio for this study is reasonable because the subject is already undergoing an S-ICD implant that includes sedation and/or anesthesia, insertion of a subcutaneous electrode and VF conversion testing. Since the standard implant and VF conversion test will be done prior to investigational procedures, it provides a high degree of assurance that the VF conversion testing is well tolerated. The protocol includes criteria to exclude subjects from the investigational testing should the initial standard of care VF conversion test suggest that the subject may be at higher risk for adverse events.

20. Safety Reporting

20.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to Boston Scientific any event which occurs in any of following categories:

- All Serious Adverse Events regardless of cause

- All Device and/or Procedure Related Adverse Events regardless whether considered serious or not
- All Device Deficiencies
- Unanticipated Adverse Device Effects (UADE) /Unanticipated Serious Adverse Device Effects (USADE) previously not defined in the physician's manual
- Certain adverse events must be reported to the sponsor in a shortened time frame, per Section 11.4.6 and 11.5.1.
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification Section 10.3), whether prior to, during or subsequent to the study procedure, must be recorded in the paper CRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

20.2. *Definitions and Classification*

Adverse event definitions are provided in Table 20-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 20-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved.

Table 20-1: Safety Definitions

Term	Definition
	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* *Ref: MEDDEV 2.7/3-2015*	Adverse event related to the use of an investigational medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the 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. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	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*	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)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

Table 20-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	**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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
Clinical Observation *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adapter 510(k) Submissions*	A clinical observation is a clinical event that did not result in invasive intervention, injury, or death, and is not an unanticipated adverse event. Corrective actions were simple adjustments such as reprogramming of the pulse generator or antibiotic treatment of a pocket infection
Clinical Complication *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adapter 510(k) Submissions*	A clinical complication is a clinical event that required an invasive intervention, injury, or death (e.g., surgical evacuation of a hematoma, lead dislodgment requiring lead repositioning, generator replacement, loss or abandonment of therapy).
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission

Table 20-1: Safety Definitions

Term	Definition
	Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

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

20.3. *Relationship to Study Device(s) and/or Study Procedure*

The Investigator must assess the relationship of the AE to the study device and/ or study procedure. See criteria in Table 20-2:

Table 20-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device, comparator or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related	The relationship with the use of the investigational device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Table 20-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Causal Relationship	The serious event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to Boston Scientific are as shown in Table 20-3.

Table 20-3: Investigator Reporting Requiremen

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE CRF 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	• Upon request of sponsor.

Table 20-3: Investigator Reporting Requiremen

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
	documentation (deidentified/ pseudonymized) for reported event.	
Serious Adverse Event	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (deidentified/pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Device Effects	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified/pseudonymized) for reported event	• When documentation is available • Upon request of sponsor
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 CRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (deidentified/ pseudonymized) for reported event.	• Upon request of sponsor

Table 20-3: Investigator Reporting Requiremen

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Adverse Event including Adverse Device Effects	Complete AE CRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through 90-day follow-up visit • Upon request of sponsor
	Provide all relevant source · documentation (deidentified/ pseudonymized) for reported event as requested by sponsor.	

Abbreviations: AE=adverse event; CRF=case report form; UADE=unanticipated adverse device effect
* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

20.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to Boston Scientific. If possible, the device(s) should be returned to Boston Scientific for analysis. Instructions for returning the investigational device(s) will be provided in the study's device management plan. If it is not possible to return the device, the investigator should document on the Device Deficiency CRF why the device was not returned and the final disposition of the device on the Investigational Device Inventory Log. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the AE CRF.

Any 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.

20.6. *Reporting to Regulatory Authorities /ECs / Investigators*

Boston Scientific is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the EC and regulatory authorities of USADE and SAE as required by local/regional regulations.

20.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific within 24 hours of site notification. The site's EC must be notified of any deaths in accordance with that site's EC policies and procedures.

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for Boston Scientific to understand the circumstance surrounding the death:

• 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, electrode, Investigational S-ICD Y-Adapter, clinical investigation, procedure, or subject condition

• Whether or not the death was witnessed

• Device status and/or activity at the time of death (device recipients only – pacing and defibrillation, active or inactive)

• Whether the subject had worsening heart failure

• Any other circumstances surrounding the death

• Approximate time interval from the initiating event to death (temporal course). Items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.

• Investigator or sub-investigator signature and date

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. Leads and related Boston Scientific RM system components (e.g., PGs) should be removed intact and returned promptly to Boston Scientific RM for analysis. The Boston Scientific Medical Safety must review information regarding subject deaths.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her 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 accepted by Boston Scientific, and approved by the site's EC, or central EC, 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 site's EC. Any modification requires acceptance from Boston Scientific prior to use of the form. The ICF must be in a language understandable to the subject and if needed, Boston Scientific will assist the site in obtaining a written consent translation. Translated informed consent forms must also have 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 at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- 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 competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/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 site 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 Boston Scientific to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. 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 applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

22. Committees

22.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation Teams review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors will further support this review. The Boston Scientific Medical Safety and Safety Trial Operations team includes health care providers with expertise in cardiovascular disease treatment and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

22.2. *Data Monitoring Committee (DMC)*

The Data Monitoring Committee (DMC) is responsible for the safety oversight of the study. The DMC will be composed of two to three members, with extensive clinical trial experience and expertise in electrophysiology and Subcutaneous Implantable Cardioverter Defibrillator

(S-ICD) implants. The DMC members will not participate in the study. The DMC will meet periodically, or as needed, to review aggregate study data and to evaluate any safety issues that may arise during the course of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

The DMC will have access to study data throughout the course of the study. If the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify both BSC and the study's Coordinating Principal Investigator. Any other DMC recommendations for study modification or termination because of concerns over subject safety will be submitted in writing to the Coordinating Principal Investigator and BSC for consideration and final decision.

23. Suspension or Termination

23.1 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 ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1 Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- Recommendation of the DMC because of concerns over subject safety.
- A decision on the part of Boston Scientific to suspend or discontinue the study per its internal business review.

23.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval

Any investigator or EC in the ASE Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston

Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 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 sites by Boston Scientific. The 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 EC terminates participation in the study, participating investigators, associated 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 a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Site

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

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to Boston Scientific unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed until the last subject completes the 90-days follow-up visit. The Principal Investigator at the site must make provision for these follow-up visits unless Boston Scientific notifies the investigational site otherwise.

24. Study Registration and Results

24.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

24.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

25. Publication Policy

Boston Scientific requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Boston Scientific study or its results. Boston Scientific may 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, Boston Scientific 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.
- Boston Scientific involvement in the publication preparation and the Boston Scientific 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.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 26-1.

Table 26-1: Abbreviations

Abbreviation/Acronym	Term
A	Ampere
2IT	Two-incision Technique
AE	Adverse Event
AF	Atrial Fibrillation
CA	Competent Authority
CRF	Case Report Form
DFT	Defibrillation Threshold
EC	Ethics Committee
EIT	Electrode Insertion Tool
EMR	Electronic Medical Record
GCP	Good Clinical Practice
HCP	Healthcare Personnel
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ISO	International Standards Organization
J	Joules
NYHA	New York Heart Association
Ω	Ohms
PG	Pulse Generator
PI	Principal Investigator
R&D	Research and Development
RM	Rhythm Management

Table 26-1: Abbreviations

Abbreviation/Acronym	Term
S-ICD	Subcutaneous ICD
TSF	Technical Source Form
UADE/USADE	Unanticipated Adverse Device Effect/ Unanticipated Serious Adverse Device Effect
V	Voltage
VF	Ventricular Fibrillation

27.2. *Definitions*

Table 26-2: Definitions

Term	Definition
DFT testing (Defibrillation Threshold testing)	Multiple VF conversion tests performed at step-wise energy level to determine the minimum shock energy needed to convert an induced VF episode
VF conversion test	A VF episode is first induced, and a defibrillation shock is then delivered to test whether the shock could convert the VF.
Source document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data.
Source data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation Note 1 to entry: This includes source data initially recorded in an electronic format.

Abbreviations are defined in Table 26.1-1.