SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Left-Ventricular Wireless Cardiac Pacing System

Device Trade Name: WiSE® (Wireless Stimulation of the Endocardium Technology) CRT System

Device Procode: SEG

Applicant's Name and Address: EBR Systems, Inc.
480 Oakmead Parkway
Sunnyvale, CA 94085

Date(s) of Panel Recommendation: None

Approval Application (PMA) Number: P240028

Date of FDA Notice of Approval: TBD

Breakthrough Device: Granted breakthrough device status on July 18, 2019, because the WiSE-CRT System met the criteria.

II. INDICATIONS FOR USE

The WiSE CRT System is indicated for adult patients who are at least 22 years of age, are indicated for cardiac resynchronization therapy (CRT), have an existing or are eligible for an implanted right ventricular pacing system, and are in one of the following two categories:

- Patients in whom previous coronary sinus (CS) lead implantation was unsuccessful, or where an implanted lead has been turned off, referred to as "**previously untreatable**";
- Patients with previously implanted pacemakers or Implantable Cardioverter-Defibrillators (ICDs) in whom standard CRT upgrade is not advisable due to known relative contraindications for CS lead or CRT device implantation, referred to as "**high risk upgrades**".

These categories are defined as follows:

Previously Untreatable:
Patients who have a full or partial CRT system and are deemed as 'previously untreatable' for one of the following reasons:

- CS lead implant was attempted but abandoned due any of the following: difficult CS access or anatomy, inadequate lead location, inadequate pacing thresholds, phrenic nerve stimulation (PNS), or other procedural challenges;
- Left ventricular (LV) lead that was implanted but not operational including patients in whom the LV lead is inoperative or programmed off due to improper function such as high threshold, non-capture, PNS, lead failure, lead dislodgement, or suboptimal LV lead location.

High Risk Upgrades:
Patients in whom standard CRT upgrade is not advisable due to known relative contraindication to CS lead implant, for example:

- Risk of venous occlusion or lesion precluding implant (e.g., multiple existing leads in situ);
- Risk of pocket infection at co-implanted device site (e.g., co-implant initial placement or battery change within last 12 months);
- Considered high risk for CS implant due to co-morbidities (e.g., history of Ischemic Cardiomyopathy or Ventricular Tachycardia (VT) with risk of epicardial pacing induced VT).

There is insufficient evidence to support the use of the WiSE CRT System in prior CRT non-responders. The safety and effectiveness of the WiSE CRT System has not been established with leadless pacemaker co-implants that utilize conductive communication (e.g., Abbott Aveir).

III. CONTRAINDICATIONS

The WiSE CRT System is contraindicated for the following:

i. Patients on triple anticoagulant who cannot tolerate peri-procedural stopping of anticoagulation therapy.
ii. Patients who cannot tolerate, or are allergic or hypersensitive to, procedural anticoagulation or contrast agents, or to the post-procedural antiplatelet regimen.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions are provided in the associated WiSE CRT System labeling.

V. DEVICE DESCRIPTION

The WiSE CRT System is an implantable, cardiac device capable of pacing the heart without a lead. The WiSE CRT System is not intended to be a life-sustaining device. A subcutaneously implanted Transmitter generates ultrasonic pulses that travel to a receiver implanted in the heart. This Receiver, also known as the Receiver Electrode or Electrode converts ultrasonic waves into electrical energy to stimulate cardiac tissue.
The WiSE CRT System applies this leadless technology to stimulate the endocardial surface of the left ventricle. Working in conjunction with standard, commercially-available implanted pacemakers (with or without leads) or defibrillators already implanted in the patient, the WiSE System replaces the pacing function of a coronary sinus lead to achieve cardiac resynchronization therapy (CRT). The WiSE CRT System synchronizes with the co-implant using sensing electrodes in the Transmitter and Battery. As the co-implant paces the right ventricle, the Transmitter generates ultrasound pulses that are received by the Electrode and converted to electrical energy to pace the left ventricle. The sequence of sensing, transmitting, receiving, and stimulating the LV is essentially simultaneous with the co-implanted device's RV pacing output and provide biventricular (BiV) pacing, an operation analogous to standard CRT pacing devices.

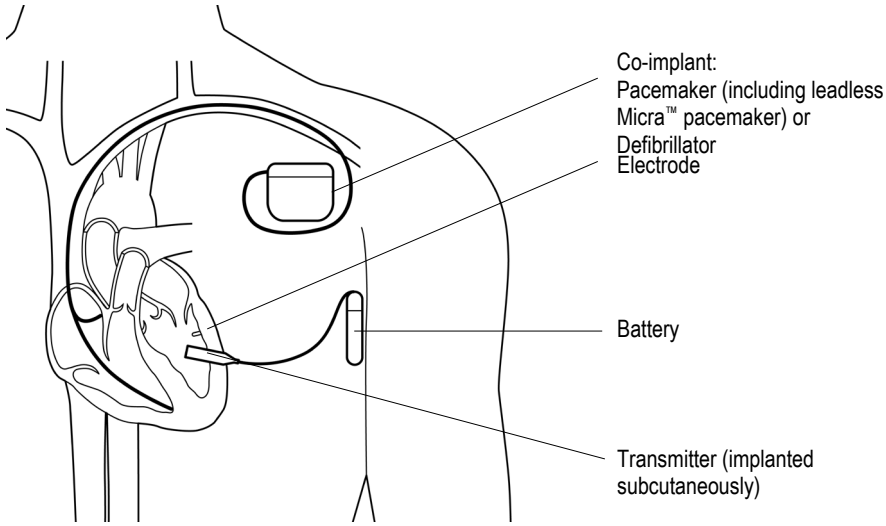
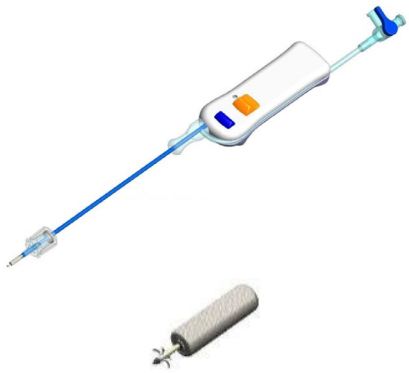


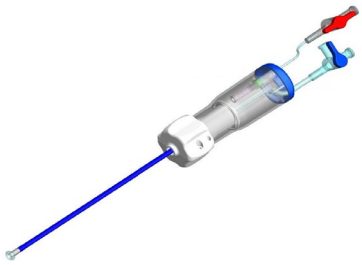
Figure 1: Implanted WiSE CRT System components with Co-Implant Device

The five main components of WiSE CRT System are summarized below:

1. **M1000 - Electrode Catheter**: A single use catheter used to implant the Electrode. The Electrode is implanted in the left ventricle; it receives ultrasound energy and converts it into electrical energy for endocardial pacing.

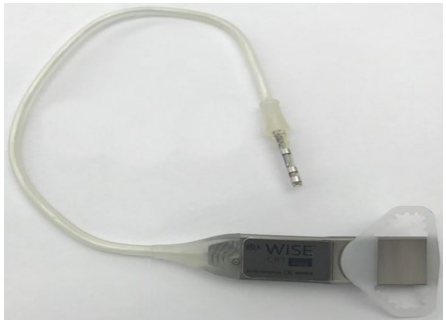


2. **M2000 - Delivery Sheath**: An acute use deflecting guiding Sheath used in combination with the Model 1000 Electrode Catheter



3. **M3100 - Battery**: A power source implanted subcutaneously int the mid-axial area of the left thorax, connected to the Transmitter by a cable.

4. **M4100 - Transmitter**: An ultrasound energy device implanted subcutaneously in the thorax.



5. **M5100 - Programmer**: An external portable touch screen tablet with a communication module used to adjust parameters on the Pulse Generator and to assist with implant and follow-up of the System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for heart failure (HF) treatment including guideline directed medical therapy (GDMT), standard application of CRT or BiV pacing, and more invasive therapies, such as a left ventricular assist device (LVAD), and eventually heart transplant. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The WiSE CRT System has not been marketed in the United States or any other country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with interventional procedures or the use of the System:

- Access site and pocket complications (e.g., pain, bleeding, infection)
- Air embolism
- Allergic reactions to materials used in the devices, sedatives, other materials and drugs used in the course of implant procedures
- Aortic/Mitral valve damage
- Arrhythmias
- Breach of Battery or Battery connections
- Cardiac tamponade/pericardial effusion
- Chronic nerve damage
- Dissection of aorta or branch vessels including femoral artery (Includes Arterial perforation)
- Early Battery depletion/malfunction
- Endocarditis
- Electronic or mechanical component failure
- Electrochemical burns
- Embolization of the non-anchored Electrode or other Delivery System material
- Excessive bleeding
- Excessive fibrotic growth

- Fluid accumulation in implant pockets
- Foreign body reaction
- General surgery and anesthesia-related risks and complications such as hypotension, hypertension, respiratory failure, syncope, cardiac failure, renal failure, anemia, and death.
- Hypersensitivity to the device materials
- Inappropriate synchronization/pacing (over-sensing, under-sensing)
- Hematoma at surgical incision, device pocket or arterial insertion sites
- High rate or competitive ventricular pacing
- Infection and/or sepsis
- Interference from other ultrasound sources that affects system performance or causes the electrode to pace
- No pacing therapy or no pacing capture leading to worsening heart failure
- Mechanical injury causing tissue damage
- Migration of device that may or may not require surgical revision
- Myocardial infarction
- Myocardial tissue injury or perforation
- Overexposure to X-ray fluoroscopic radiation - Radiation skin burns
- Phrenic nerve stimulation leading to diaphragmatic pacing
- Pneumothorax
- Psychological disturbances (dependency, depression, fear of Battery depletion, fear of malfunction)
- Reset of programmed device parameters
- Skin erosion overlying implanted device
- Septal defect
- Stroke or transient cerebrovascular episodes
- Thermal tissue injury from Transmitter elements
- Thrombus formation and thromboembolism

For the specific adverse events that occurred in the clinical study, please see Section X.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

i. Bench top testing

Nonclinical testing of the WiSE System CRT was conducted to ensure the finished device performs in accordance with their design specifications. Table 1 outlines the key tests.

Table 1: Summary of Key Tests performed on the WiSE CRT System

Test	Test Description / Acceptance Criteria	Results
System		
System Compatibility	Functional tests assessed the ability of the connections between various component of the WiSE CRT System to properly communicate	Pass
Mechanical Shock and Vibration	To evaluate the mechanical performance and safety of the system when subjected to mechanical shock and vibration conditions in compliance with ISO 14708-2 Shock: A total of 6 shocks, One along each of the 6 axes. Each shock was 1ms in duration and 500g in amplitude. The device was also subjected to random vibration for 30 minutes on 3 perpendicular axes	Pass
Pressure	To evaluate the device safety and functionality subject to 25 cycles of low	Pass

Test	Test Description / Acceptance Criteria	Results
	pressure and 40 cycles of high pressure in compliance with ISO 14708-2	
Corrosion	To evaluate corrosion resistance of the blood and tissue contacting materials chosen for the devices of the WiSE CRT System. Electrode, Battery, and Transmitter, corrosion testing per ISO 14708-1. Delivery System testing per ISO 10555-1.	Pass
Electromagnetic Compatibility (EMC)	Transmitter: To evaluate the ability of the system to function safely and effectively in its intended electromagnetic (EM) environment, including immunity to EM disturbances, without introducing excessive EM disturbances that might interfere with other equipment. The device shall meet the applicable requirements of ISO 14708-1, ISO 14708-2 and ISO 14117 Programmer: To verify Electromagnetic Compliance (EMC), in terms of radiated and conducted electromagnetic interference, and susceptibility to radiated fields and electrostatic discharge, shall be tested in accordance with IEC 60601-1-2	Pass
EMI-EAS, RFID, Tag deactivators, Metal Detectors	To evaluate the function of the system to function safely and effectively in electromagnetic (EM) environments including Electronic Article Surveillance systems, radiofrequency identification systems and Metal Detector systems	Pass
Safety-Exposure to Electrosurgery	To evaluate the safety and functionality of the device subject to electrosurgery conditions as specified by the applicable clauses of ISO 14117 standard	Pass
Safety-Exposure to External Defibrillation	To evaluate the device safety and functionality with regard to exposure to external defibrillation condition as specified by the applicable clauses of ISO 14117 standard	Pass
Safety-Ultrasound	To evaluate the device safety and functionality with regard to exposure to Ultrasound as specified by the applicable clauses of ISO 14708-1	Pass
Safety-Protection against device heat generation	To verify the outer surface of the device shall not be greater than 2˚C above the normal surrounding body temperature of 37˚C when implanted in normal operating mode as specified per ISO-14708-1	Pass
Hermeticity Leak Test	To verify that the Transmitter enclosure meets the hermeticity requirements of MIL-STD 883 Method 1014	Pass
Radio Communications	To verify that the system complies with United States Radio communication requirements 47 CFR Part 15. **Implanted Transmitter:** **FCC ID: 2AMRX-4100)** MICS (Medical Implant Communication Service): 402-405 MHz Rated RF Power Output: 1.585 µW Receiver Specification: 2443 MHz – 2457 MHz (Receive Only) **External Programmer:** **FCC ID: 2AMRX-5100** RF Reception Band: 402-405 MHz (MICS Medical Implant Communication Service/ MedRadio rules) RF Transmission Bands Frequency: 402.15 - 404.85 MHz (MICS/ MedRadio band) Modulation: 2-FSK @ 200 kbps Effective Radiated Power: -16 dBm maximum Frequency: 2.443 - 2.457 GHz (ISM band)	Pass

Test	Test Description / Acceptance Criteria	Results
	Modulation: Manchester-encoded OOK (100%) Effective Radiated Power: + 20 dBm maximum	
Physical Dimensions		
Transmitter	To evaluate the following physical dimensions of the Transmitter: Volume: The Transmitter with Battery connection cable shall have a maximum volume of 15 cubic cm, with at most 8 cubic cm for the enclosure and 7 cubic cm for the cable Mass: 30 grams Battery Connection Cable Length (Nominal): 30 cm	Pass
Electrode	Volume: 0.05 ml Body Length: 9.2 mm Diameter: 2.8mm Cathode Area: 0.9 mm^2 Anode Area: 82 mm^2 Cathode-Anode Spacing: 2.8 mm Needle/Anchor Length: 3.5 mm	Pass
Battery	Volume (Enclosure and Header): 54 ml Width x Height x Thickness: 48.7 x 111.1 x 11.4 mm Mass: 93 g	Pass
Electrode Delivery System	Effective Length Sheath: 109.5 cm Effective Length Catheter with Electrode: 124 cm Length of Deflectable Section: 15 cm Max Sheath Outer Diameter: 4.0 mm/ 12 F Max Balloon Diameter: 8 mm	Pass
Programmer	Tablet Computer (H x W x T): 20.3 cm x 31.2 cm x 2.4 cm Radio Module Footprint (W x L) / Height: 7.4 cm x 9.4 cm / 13.0 cm Mass (Tablet / Radio Module): 1.3 kg / 0.3 kg Radio Module Cable Length: 3.0 meters AC/DC Power Adapter/ Cord Length: 3.8 meters Marker Events Cable Length: 3.0 meters	Pass
Receiver Electrode		
Mechanical	To verify fixation tine and piezoelectric material fatigue integrity and strength of welds and other connections To verify hermeticity of the electrode	Pass
Electrical	To verify acoustic response and generation of electrical pulse.	Pass
Corrosion	To verify corrosion resistance per ASTM F2129	Pass
Transmitter		
Mechanical	To verify header and can integrity and cable fatigue performance	Pass
Battery		

Test	Test Description / Acceptance Criteria	Results
Nominal Battery Capacity:	15 Ah (150 KJ)	Pass
UN Test ST/SG/AC.10/11	To verify that the Battery complies with applicable requirements of UN Test ST/SG/AC.10/11	
Discharge Testing	To verify the Battery capacity Beginning of Service to End of Service at 37ºC through accelerated discharge testing	Pass
Self-Discharge Rate	To verify self-discharge rate when stored at 20ºC ± 2ºC	Pass
Electrode Delivery System		
Mechanical	Max Balloon Pressure: 496 kPa Max Rated Injection Pressure Pigtail Catheter: 800 kPa Max Rated Injection Pressure Sheath: 400 kPa Max Rated Injection Pressure Electrode Catheter: 800 kPa	Pass
Delivery System Corrosion	To verify that the Delivery System meets corrosion resistance requirements listed in ISO 10555-1.	Pass
Delivery System Tensile	To evaluate the tensile strength (e.g. RE to Delivery System, Reference Needle, Delivery Sheath Shaft) of the delivery system meets the applicable requirements listed in ISO 10555-1	Pass
Delivery System Deflection	Max Deflection: 120° (minimum) Curve Radius at 90°: 6.5 cm (inner radius)	Pass
Programmer		
Electrical	AC Line Voltage: 100-240 VAC Power Input: 1.6 A @ 100 VAC AC Frequency: 50/60 Hz	Pass
Safety	To verify that the Programmer meets the applicable safety compliance requirements identified in IEC 60601-1	Pass
Cleaning	To verify that the surfaces and enclosures of the programmer shall be compatible with wiping with isopropyl alcohol or mild detergents for cleaning and disinfecting	Pass

ii. Software Verification and Validation

Software/Firmware was developed according to IEC 62304. Documentation includes software level of concern, software description, risk analysis, software requirements specification, software architecture diagrams, software design specifications, requirements traceability matrix, software development environment description, verification and validation documentation, revision level history, unresolved anomaly report, and cybersecurity documentation.

a) Transmitter Firmware
   Verification of all Transmitter firmware was conducted to ensure firmware was tested to its specified requirements. Testing occurred at the unit, integration, and system level. Firmware verification testing was successfully completed and demonstrated that Transmitter firmware meets its requirements.
b) Programmer Software
   Verification of all Programmer software was to ensure the software was tested to its specified requirements. Testing occurred at the unit, integration, and system level. Software verification testing was successfully completed and demonstrated that Programmer software meets its requirements.
c) Cybersecurity

Cybersecurity was verified and documented according to FDA Guidance Document, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices Guidance for Industry and Food and Drug Administration Staff".

iii. Biocompatibility

Biocompatibility testing was performed for patient-contacting components of the WiSE CRT System in accordance with ISO 10993-1, *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*, on the finished sterilized devices. All required biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The WiSE CRT Electrode is classified as a long term (> 30 days) permanent implant with circulating blood contact. The WiSE CRT Battery and Transmitter are classified as long term (> 30 days) permanent implants with tissue contact. The WiSE CRT Delivery Catheter and Delivery Sheath are classified as limited contact (≤ 24 hours) devices with externally communicating circulating blood contact. The WiSE CRT Reference Needle is classified as limited contact (< 24 hours) device with externally communicating tissue contact. Results demonstrated that the System is biocompatible for the intended use.

iv. Sterilization

The WiSE CRT System components that are provided sterile (Electrode Catheter, Delivery Sheath, Battery, and Transmitter) are terminally sterilized using a 20% ethylene oxide (EO) and 80% Carbon Dioxide (CO2) sterilization process to provide a minimum sterility assurance level (SAL) of 10-6. Validation of the sterilization process is in compliance with ANSI/AAMI/ISO 11135-1, *Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices*. Sterilant residuals conform to the maximum allowable limits of Ethylene oxide and ethylene chlorohydrin (ECH) residuals as specified in ISO 10993-7, *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*.

v. Packaging and Shelf Life

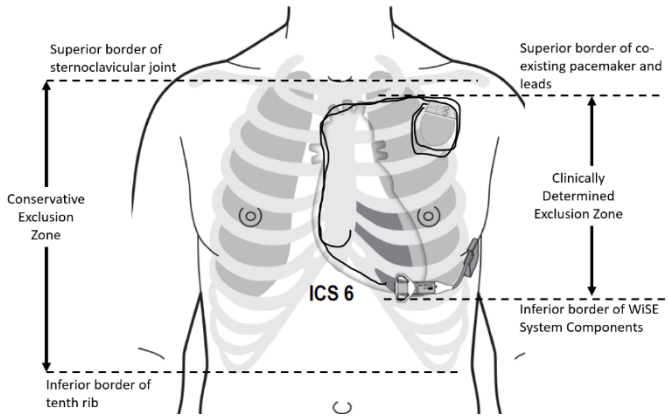
Packaging and shelf-life validations for the Electrode Catheter, Delivery Sheath, Battery, and Transmitter was completed in compliance with ISO 11607-1 Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems and packaging systems. Shelf life for the sterile components has been established as 1 year.

Packaging validation for the non-sterile Programmer was completed per clause 7.9.3.1 of IEC 60601-1: 2020, *Medical Electrical Equipment – Part 1: General requirements for basic safety and essential performance*.

All packaging validations were done on devices which went through environmental conditioning, distribution conditioning and accelerated aging (for sterile products only). The packaging validation was successfully completed, which demonstrated that the packaging protects the device during transportation and storage.

vi. Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing results demonstrate that the implanted devices (Electrode, Battery and Transmitter) of the WiSE CRT System are MR Conditional under specified conditions in table below.

Parameter	Conditions of Use
Static Magnetic Field Strength (B_0)	1.5 T, 3 T
Type of Nuclei	Hydrogen
Static Magnetic Field (B_0) Orientation	Horizontal, cylindrical bore
Maximum Spatial Field Gradient	20 T/m (2000 gauss/cm)
Maximum Switched Gradient Slew Rate per Axis	200 mT/m/ms
Maximum Switched Gradient Amplitude per Axis	45 mT/m
RF Polarization (RF Excitation)	Multichannel-2 (MC-2) or circular polarization (CP)
RF Transmit Coil Type	• No local RF transmit coils inside the exclusion zone. • No restrictions on RF transmit coil type when placed outside of the exclusion zone.
RF Receive Coil	Any receive RF coil may be used.
MR System (RF) Operating Mode or Constraints	• 1.5 T: Normal operating mode • 3 T: Normal operating mode
Maximum Whole-Body Specific Absorption Rate (SAR)	2 W/kg (normal operating mode)
Maximum Head SAR	3.2 W/kg (normal operating mode)
Anatomy Scan Region Restrictions	Any scan landmark is acceptable with the exclusion zone placed outside the MR bore.  The exclusion zones are defined as follows:

Parameter	Conditions of Use
	▪ Conservative Exclusion Zone: It extends from the superior border of the sternoventricular joint to the inferior border of the 10th rib. OR ▪ Clinically Determined Exclusion Zone: It is based on the actual location of the implanted components and determined by palpation of the implanted WiSE CRT System and the co-implanted pacemaker system or by X-ray imaging. The conservative exclusion zone must be used if the implanted components cannot be unambiguously identified.
Patient Characteristics	▪ Scanning patients who have multiple MR Conditional items present is acceptable as long as the MR labeling conditions for all items can be satisfied. ▪ The patient has no broken leads from the co-implanted pacemaker or leads with intermittent electrical contact, as confirmed by lead impedance history.
Patient Position in Scanner	It is mandatory that the MR exclusion zone defined above is observed.
Item Configuration	The following configurations are allowed to enter the MR environment: ▪ A WiSE CRT System with all components implanted. ▪ A WiSE CRT System with a subset of components implanted. ▪ The implanted WiSE CRT System is implanted with a co-implanted pacemaker system. MR scans are only allowed if the co-implanted pacemaker is also MR Conditional. In addition to the conditions listed above for the implanted WiSE CRT System, all MR scan conditions for the co-implanted MR Conditional pacemaker must be met as well.
Scan Duration	2 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back-to-back series/scan without breaks) in compliance with the exclusion zone
Required Programming Setting	The following programming has to be completed before the patient enters the MR environment: ▪ Implanted WiSE CRT System to OFF-mode and ▪ Co-implanted pacemaker MRI Conditional implant

Parameter	Conditions of Use
	mode enabled
Instructions to be Followed Before, During, or After the MRI Exam	The following has to be completed after the patient leaves the MR environment: ▪ The WiSE CRT System and the co-implanted pacemaker programmed to their pre-scan settings. ▪ A system check of the WiSE CRT System and the co-implanted pacemaker to ensure safe operation.

B. Animal Studies

EBR has conducted in vivo animal studies on goats using the WiSE CRT System devices in order to evaluate the acute and chronic performance and safety of the system in the animal model. These studies were non Good Laboratory Practice (GLP) studies.

i. 30-day, 45-day and 90-day Chronic Electrode Implant Study

A study was conducted to assess the safety of chronic implantation of the Receiver Electrode (RE) component of the WiSE CRT system. A total of 33 REs were implanted into the Left Ventricles of 17 goats such that each of 16 goats were implanted with two REs and the remaining 1 goat was implanted with one RE. The primary objective of this safety study was to determine the time course and the extent of device coverage for endothelialization of the devices in the Left Ventricle. The secondary objective of the study was to assess the chronic attachment of the devices. The end time-points selected were 90 days ± 7 days (13 goats), 45± 5 days (two goats), and 30 days ± 3 days (two goats). The histopathological evaluations demonstrated that the REs implanted in the Left Ventricle were tolerated in the hearts of goats at 30, 45, and 90 days post implantation. Complete endothelialization was evident in the two 30 day animals. No REs were embolized.

ii. Chronic Electrode Pacing Sub-Study

The Chronic Electrode Pacing study was a sub-study of the Chronic Electrode Implant study described above. In this study, the pacing capture threshold (PCT), which is the minimum pacing energy required to produce a depolarization of the left ventricle by the RE, was evaluated in 5 goats that had been implanted with functional REs in the left ventricle during the Chronic Electrode Implant study. The objective of this pacing study was to observe whether any changes occur in PCTs from the time of implant through maturation of connective tissue at the interface between tissue and the cathode of the RE. The PCTs were evaluated at implant and at up to four time points following implantation: 4-6 days, 11-13 days, 27-29 days and 42 days.RE PCT were stabilized in two to six weeks post implantation in the goat model.

iii. Acute and Chronic Delivery Catheter Safety Study

An acute and chronic Delivery Catheter Safety study was conducted to obtain

evidence that the WiSE-CRT Delivery System (Model 1000 Catheter and Model 2000 Sheath) can be used to safely implant the RE in the endocardium of the left ventricle in goats.

A total of 53 Catheters were inserted into Sheaths under conditions of nominal implant and simulated failures. 42 of the 53 total REs were implanted consecutively in 42 delivery attempts into the left ventricles of 10 goats. The 10 goats included 8 acute goats (N= 34 electrodes) and 2 chronic goats that were survived for 30-days prior to necropsy (N= 8 electrodes). The remaining 11 delivery systems were used for simulating failure modes or for removal of the REs after it was anchored but not yet released. At necropsy, all REs were embedded with no evidence of excessive tissue trauma or injury. No REs were dislodged or embolized. REs were able to be removed by the Delivery System.

iv. Chronic System Validation in Animals

The System Validation in Chronic Animals study was conducted to obtain evidence that the WISE CRT System can be used to synchronize to a co-implant pacing pulse and to chronically capture the LV.

The objective of the study was to demonstrate system functionality while emulating use of the system with chronically implanted Electrodes and Pulse Generator Systems in their final designs. Two adult goat models were implanted with Receiver Electrodes, Model 4000 Transmitters and Model 3000 Batteries in their final design forms. One goat was implanted for 110 days, and the other was implanted for over 600 days. Follow-up procedures, emulating the use of the Programmer (Model 5000) during clinical follow-up, were used to validate complete system operation in the chronically implanted animals throughout the implantation period.

In this study, the WiSE CRT System provided consistent chronic detection of the co-implant RV pacing output, searching for and targeting the RE, transferring ultrasound energy to the RE, pacing capture of the LV with the Electrode, and optimizing system parameters by testing/programming parameters through the radio link of the Programmer.

v. System Validation using Model 4100 Transmitter

The System Validation using Model 4100 Transmitter study was conducted to obtain evidence that the functional and performance requirements of the WiSE-CRT system are satisfied using the Model 4100 Transmitter.
The study was conducted on one adult goat model which had been implanted with the RE, Battery (Model 3000) and Model 4100 Transmitter for 170 days. The WiSE-CRT system using the Model 4100 Transmitter satisfied functional and performance requirements meeting the validation test acceptance criteria in the protocol.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the WiSE CRT System for the delivery of BiV pacing for CRT in patients with advanced HF in the US, European Union, United Kingdom, and Australia under IDE #G150244. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

The SOLVE-CRT Study was a prospective, multi-center, multi-national clinical evaluation of the WiSE CRT System. The treated population included patients who had previously failed conventional CRT, who had not responded to conventional CRT, or who were high risk upgrades (HRU) for conventional CRT. The study was a global trial including investigational sites from the United States (US), European Union (EU), United Kingdom (UK), and Australia (AU).

A. Study Design

Patients were treated between January 17, 2018, and February 9, 2023. The database for this PMA reflected data collected through February 15, 2023, and included 214 patients. There were 68 investigational sites.

The SOLVE-CRT Study was a prospective pivotal clinical trial comprised of three separate, multi-center, multi-country parts:

- Part I Roll-In (n=31), single-arm, open label
- Part II Randomized (n=108), two-arm, randomized 1:1, double-blind
- Part III Single-Arm (n=75), single arm, open label

Part I Roll-In of the Study was introduced to provide physicians with implant experiences prior to enrolling patients in the Randomized Part of the trial. After enrolling 31 participants, the Roll-In Part was concluded as the results demonstrated low complication rates. Enrollment into Part II Randomized was affected by the COVID-19 pandemic and was paused in March 2020 after 108 patients were enrolled at 36 centers. The trial was modified to include a Single-Arm, non-randomized Part to complete the study (Singh 2021).

All Part II Randomized participants underwent implantation of the WiSE CRT System which was initially programmed to 'Off. The participants in Part II Randomized were then assigned, employing a 1:1 randomization, to either the Treatment arm ('WiSE On') or the Control arm ('WiSE Off'). After 6 months of follow-up, the Control arm patients would cross over to the Treatment arm. Part I Roll-In participants and Part III Single-Arm participants were programmed to 'WiSE On' following the procedure. All patients in Parts I, II, and III adhered to the same 6-month follow-up schedule.

Participants were followed-up for six months after implantation of the WiSE CRT System for primary endpoint analyses. Primary endpoint analyses were from the pivotal Parts of the Study—Part II (Randomized) and Part III (Single-Arm).

The trial used an independent Clinical Events Committee (CEC) and a Data Safety Monitoring Board (DSMB):

Clinical Events Committee (CEC)

A CEC was established to provide independent review and adjudication of adverse events (AEs) reported during the investigation. The CEC consisted of five medical experts relevant to HF, CRT, and electrophysiology including the CEC chairperson. They were independent of the Sponsor and study investigators, and do not have any significant investment in the Sponsor.

Data Safety Monitoring Board (DSMB)

A DSMB was established to assess the continuing safety of participants, ongoing scientific integrity of the Study and effectiveness of the study device. The DSMB consisted of five non-EBR employed physicians and scientists who were not participating investigators for the Study, including a DSMB Chairperson.

1. **Clinical Inclusion and Exclusion Criteria**

Inclusion Criteria

Enrollment in the SOLVE-CRT Clinical Trial study was limited to patients who met the following inclusion criteria:

	Inclusion Criteria
1	Patient with a class I or IIa (1) or (2) indication for implantation of a CRT device according to current available guidelines (with additional QRS criteria on Class IIa (1)):
	a. Class I: NYHA II, III, IV, EF ≤ 35%[1], LBBB, QRS ≥ 150ms[2]
	b. Class IIa (1): NYHA II, III, IV, EF≤ 35%, LBBB, QRS ≥ 130 to < 150ms
	c. Class IIa (2): NYHA II, III, IV, EF≤ 35%, non-LBBB, QRS ≥ 150ms
2	Patient is a:
	a. 'Non-responder' (Part I and Part II - Roll-in and Randomized Only): [This criterion is not applicable to Part III Single-arm]: Patients who have a CRT system that is functional and despite an adequate trial of Guideline Directed Medical Therapy (GDMT) [1] and attempts at optimal device programming [2] the patient has not responded to therapy for a minimum of 6 months. Non-response is defined as:
	i. EF has remained unchanged or worsened (defined as < 5% increase since implant), and

[1] Source documentation should be provided to support non-response despite trial of GDMT which should include an angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB), or angiotensin receptor–neprilysin inhibitor (ARNI) in conjunction with evidence-based beta-blocker therapy and aldosterone antagonists, or other cardiac medications (e.g., diuretics, nitrates, digitalis, etc.) that were attempted (Yancy 2013; Yancy 2017). ACEI, ARB or ARNI and beta blocker, aldosterone blockade should be at a stable dose for 30 days. During the 30-day period immediately preceding enrollment, daily dose may increase by no more than 100% from the dose at the beginning of the 30-day stability period and may decrease by no more than 50% from the dose at the beginning of the 30-day stability period.

[2] Attempts at programming for high percentage of BiV pacing and optimization of timing intervals should have been attempted and must be documented.

	Inclusion Criteria
	ii. The patient's clinical status based in the totality of available clinical evidence (such as NYHA Class, exercise tolerance, QOL, or global assessment) has remained unchanged or worsened, as determined by the local Site Enrollment Committee
	b. 'Previously Untreatable' (Part I, Part II, and Part III- Roll-in, Randomized, and Single-arm): Patients who have a full or partial CRT system, who meet general inclusion criteria and are deemed as 'previously untreatable' for one of the following reasons:
	i. Patients in whom CS lead implantation for CRT has failed
	CS lead implant was attempted but abandoned due any of the following: difficult CS access or anatomy, inadequate lead location, inadequate pacing thresholds, persistent phrenic nerve pacing, or other procedural challenges
	ii. CS lead implanted but has been programmed OFF[1]
	LV lead that was implanted but not operational includes patients in whom the LV lead is inoperative or programmed off due to improper function such as high threshold, non-capture, phrenic nerve pacing, lead failure, lead dislodgement, or sub-optimal LV lead location
	c. High Risk Upgrade' (Part I, Part II, and Part III): Patients in whom standard CRT upgrade is not advisable due to known relative contraindication to CS lead implant, for example:
	i. Risk of venous occlusion or lesion precluding implant (e.g., multiple existing leads in situ)
	ii. Risk of pocket infection at co-implanted device site (e.g., co-implant placement or battery change within last 12 months)
	iii. Considered high risk for CS implant due to co-morbidities (e.g., history of ICM or VT with risk of epicardial pacing induced VT)
3	Patients on a stable Guideline Directed Medical Therapy (GDMT)
4	Patient must be 18 years old or over
5	Patient has signed and dated informed consent
6	Patient has suitable anatomy for implant of the WiSE CRT System (e.g., adequate acoustic window, LV wall thickness in target implant area ≥ 5 mm, absence of LV wall structural abnormalities which may preclude implant),

Exclusion Criteria

Patients were excluded from the SOLVE-CRT Study if they met any of the exclusion criteria in the table below.

	Exclusion Criteria
1	Pure RBBB
2	LVEDD ≥ 8cm
3	Non-ambulatory or unstable NYHA class IV
4	Contraindication to heparin, chronic anticoagulants, or antiplatelet agents

	Exclusion Criteria
5	Triple anticoagulant patients who cannot tolerate peri-procedural stopping of anticoagulation therapy
6	Attempted device implant (pacemaker, ICD, CRT, LV lead) or successful co-implant within prior 30 days.
7	Patients with planned or expected lithotripsy treatment post implant
8	Life expectancy of < 12 months
9	Chronic hemodialysis
10	Stage 4 or 5 renal dysfunction defined as eGFR < 30
11	Grade 4 mitral valve regurgitation
12	Noncardiac implanted electrical stimulation therapy devices
13	Patients with a prosthetic aortic valve and a non-viable transseptal approach for the electrode implant
14	Patients with a prosthetic mitral valve and a non-viable retrograde aortic approach for the electrode implant
15	Unstable angina, acute MI, CABG, or PTCA within the past 1 month
16	Correctable valvular disease that is the primary cause of heart failure
17	Recent CVA or TIA (within the previous 3 months)
18	Patients with a history of paroxysmal or persistent atrial fibrillation/flutter are excluded if they have had a documented AF episode > 30 min or a cardioversion in the past 30 days from screening.
19	Patients with permanent AF are excluded if they have intact AV node conduction (RV pacing < 95%)
20	Already included in another clinical study that could confound the results of this study
21	Pregnancy
22	Known drug or alcohol addiction or abuse
23	Moderate or severe aortic stenosis
24	Participant unable to attend follow-up at the investigative center or unable, for physical or mental reasons, or to comply with the trial's procedures
25	For Part II randomized patients, those who will not tolerate being randomized to the Control Group for 6 months

2. Follow-up Schedule

All participants had to meet the Inclusion/ Exclusion criteria and undergo a screening transthoracic echocardiograph (TTE) to assess left ventricular (LV) wall thickness and presence of adequate acoustic windows for implantation of the WiSE CRT Transmitter. All assessments and procedures had to be done within 45 days before implant, except NT-proBNP which was required < 24 hours prior to implant of the first WiSE CRT System device. For Part I Roll-In and Part II Randomized in CIP v1.9

and prior versions, the required window was within 30 days prior to implant.
A post-implant visit (< 24 hours from implant) was required per clinical investigation plan (CIP) v1.9 and prior versions, but it was subsequently removed from CIP v2.0.

Pre-Discharge
In Part II Randomized, participants who had a successful WiSE CRT System implant were randomized to one of the two arms, Treatment or Control, prior to discharge. All assessments and procedures, including randomization, had to be completed within 7 days after implant. For the Part III Single-Arm patients, the visit at six months was ± 20 days.

Follow-Up Visits
Participants were followed up at one month (± 21 days), three months (± 15 days), six months (± 15 days), 12 months (± 45 days), 18 months (± 45 days), 24 months (± 45 days) and then annually through five years (± 60 days) from the time of Electrode implant. For the Part III Single-Arm patients, the visit at six months was ± 20 days.
For Part II Randomized, participants were unblinded at the six-months visit after all assessments and procedures were completed. The 24-hour ambulatory Holter monitor was required for the first consecutive 125 participants in the Randomized Treatment arm. Subsequently, this assessment was removed from CIP version 2.0.
The required assessments and procedures are outlined in Table 2.

Table 2. SOLVE-CRT Schedule of Study Assessments

	Pre-Implant	Pre-Discharge	1M	3M	6M	12M	18M	24M	3-, 4-, 5-Years
Time frame for visits/ assessments (calculated from date of last WiSE CRT System Component implant – e.g., Electrode)	Within 45 days pre-implant	0-7 days	± 21 days	± 15 days	± 20 days	± 45 days	± 45 days	± 45 days	± 60 days
Eligibility	X								
Acoustic Window Screening	X								
Physical Exam	X	X	X	X	X	X	X	X	X
Laboratory	X	X	X	X	X	X	X	X	
NT-proBNP	X				X				
Cardiac Medications	X	X	X	X	X	X	X	X	X
Chest X-Ray		X							
12-Lead ECG	X				X	X		X	
KCCQ QOL	X			X	X	X	X	X	X
NYHA Functional Class	X			X	X	X	X	X	X
Echocardiogram	X				X	X		X	
WiSE CRT System and Co-implant Device Check	X	X	X	X	X	X	X	X	X
Randomization (Part II Only)		X							
Planned Cross-over (Part II Control Arm Only)					X				
24-hour Holter Monitor (Part II Only)					X				

3. Clinical Endpoints

Per the CIP, the Study was considered a success when both the primary safety endpoint and the primary Effectiveness endpoint were achieved. Success was evaluated using a group sequential design with one interim safety analysis.

1. Fixed sample size Effectiveness analysis and interim safety analysis after completion of six-month follow-up of all Part II and first 75 Part III participants
2. Final safety analysis after completion of follow-up of final 117 Part III participants

Primary Safety Endpoint (Part II and Part III)

The primary Safety endpoint for the SOLVE-CRT Study was freedom from Type I complications at six months post implant compared to a performance goal of 70% for all participants in Part II and Part III of the Study (n = 183). Type I complications included AEs caused by any component of the investigational system or specific procedure-related events.

The null and alternative hypotheses:

$$H_o: p \leq 70\% \text{ vs } H_a: p > 70\%$$

where 70% is the objective performance criterion and p the percentage of patients who are free from Type I complication at six months.

The analysis consisted of calculating a one-sided lower bound from the exact binomial distribution and comparing the lower bound to the performance goal. The width of the confidence interval was determined by the nominal alpha at the interim analysis.

Primary Effectiveness Endpoint (PU-HRU of Part II and Part III):

The primary Effectiveness endpoint for the SOLVE-CRT Study was the mean relative (%) change in Left Ventricular End-Systolic Volume (LVESV) as assessed by echocardiography at six months post implant compared to a performance goal of -9.3%. All echocardiograms were evaluated by a blinded echocardiographic core lab. The relative (%) mean change in LVESV from baseline to six months was calculated as follows:

$$\frac{\sum_{i=1}^{n}((x_{i\,LVESV6m} - x_{i\,LESVbl})/\, x_{i\,LVESVbl}) * 100\%}{n}$$

The null and alternative hypotheses:

$$H_o: \mu_{txt} \geq -9.3\% \text{ vs } H_a: \mu_{txt} < -9.3\%$$

where μ_{txt} is the mean % change in LVESV in the Treatment arm from baseline through six months.

The comparison of the mean % change in LVESV to the performance goal of -9.3% was based on the upper bound of a 95% two-sided confidence interval (CI) constructed for the estimated mean change using the t-distribution. The estimated upper bound of the confidence interval was compared to the performance goal. If the upper bound was less than 9.3%, then this endpoint was successfully achieved.

Secondary Effectiveness Endpoints (PU-HRU of Part II and Part III)

The secondary Effectiveness endpoints were based on the Effectiveness population at

six months post implant. No formal testing of the secondary Effectiveness endpoints was performed. All secondary endpoints were summarized with descriptive statistics. Secondary Effectiveness endpoints included the proportion of participants with an acoustic pacing capture threshold (APCT) less than 2.9 mJ, the proportion of participants with APCT stability (defined as a less than a 3x relative change in APCT from baseline), percent BiV pacing, ejection fraction (EF) responder analysis for ≥ 5% absolute increase, and Kansas City Cardiomyopathy Questionnaire (KCCQ) responder analysis for ≥ 5 points absolute increase.

B. Accountability of PMA Cohort

At the time of database lock, a total of 214 patients were enrolled in the PMA Study across 68 international centers in four geographies (US, EU, UK, AU). For the interim analysis at six months post implant, data included all (100%) of the 183 participants from Part II and Part III of the Study.

Patient Disposition & Analysis Groups

The Safety population was made up of all 108 patients enrolled in Part II (Randomized) and 75 participants enrolled in Part III (Single-Arm) of the Study.

For the Effectiveness analysis, only a portion of participants from Part II who represented the same population as those in Part III were included in the Effectiveness analysis. As such, the Effectiveness population was made up of 25 previously untreated (PU) and High-Risk Upgrade (HRU) participants who were randomized to the Treatment arm of Part II and 75 PU and HRU participants from Part III.

PU patients had a full or partial CRT system but were not receiving CRT because of a failed LV lead implantation or other lead issue. HRU patients included those in whom standard CRT upgrade was not advisable due to known relative contraindication to coronary sinus lead implant.

Figure 2 provides a patient accountability tree with patient disposition and analysis populations for the interim analysis of the SOLVE-CRT Study.

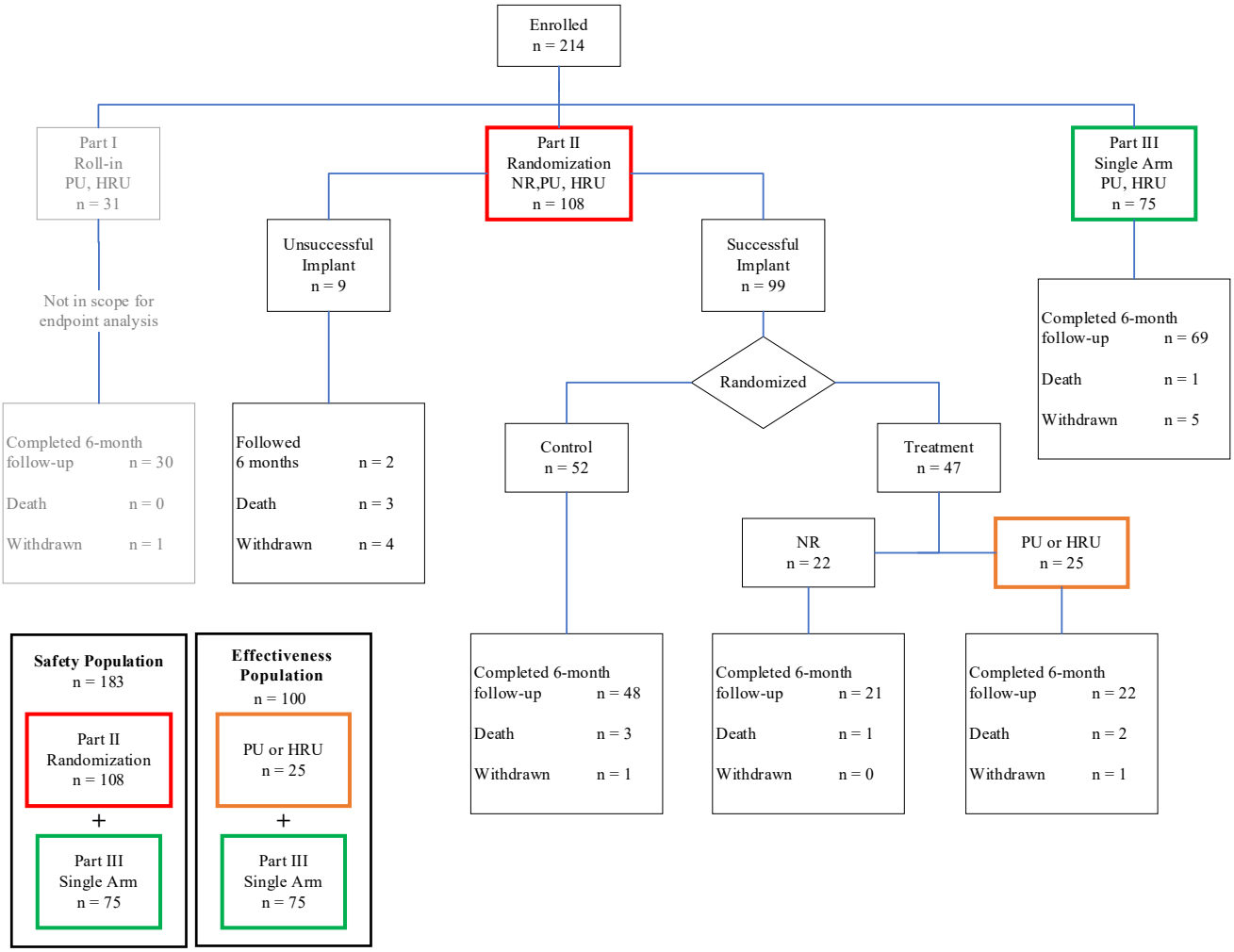


Figure 2. Patient Disposition and Analysis Groups

C. Study Population Demographics and Baseline Parameters

Baseline CRT Indication

The demographics and baseline characteristics of the study population were comparable to the population indicated for CRT. Indication classes were defined as:

- Class I: NYHA II, III, IV, EF ≤ 35%, LBBB, QRS ≥ 150ms
- Class IIa (1): NYHA II, III, IV, EF≤ 35%, LBBB, QRS ≥ 130 to < 150ms
- Class IIa (2): NYHA II, III, IV, EF≤ 35%, non-LBBB, QRS ≥ 150ms

As shown in Table 3, indications for CRT in the Safety population were Class I (68.9%), Class IIa (1) (13.7%), and Class IIa (2) (17.5%). Twenty-four percent (24%) of participants in the Safety population were Non-Responders (NRs), 60.1% were PUs, and 15.8% were HRUs.

For the Effectiveness population, indications for CRT were Class I (64.0%), Class IIa (1) (14.0%), and Class IIa (2) (22.0%). Seventy-five percent (75.0%) of participants in the

Effectiveness population were PUs and 25.0% were HRUs.

Table 3. Indications for CRT

Indication	Safety Population (N=183) n/N (%)	Effectiveness Population (N=100) n/N (%)
Class I	126/183 (68.9%)	64/100 (64.0%)
Class IIa (1)	25/183 (13.7%)	14/100 (14.0%)
Class IIa (2)	32/183 (17.5%)	22/100 (22.0%)
Non-Responder	44/183 (24.0%)	0/100 (0.0%)*
Previously Untreatable	110/183 (60.1%)	75/100 (75.0%)
Failed CS lead implant	68/183 (37.2%)	48/100 (48.0%)
CS lead turned off	42/183 (23.0%)	27/100 (27.0%)
High Risk Upgrade	29/183 (15.8%)	25/100 (25.0%)

Patient Enrollment by Geography

The SOLVE-CRT Study was a global trial including patients enrolled in the United States (US) and Outside United States (OUS). Table 4 summarizes the geographic region of participants in the Study. Of the 183 total enrolled patients, 92 (50.3%) patients were from the US and 91 (49.7%) patients were from OUS. In the Effectiveness population, the majority of the patients enrolled were from US (73, 73%) vs OUS (27, 27%).

Table 4. Patient Enrollment by Geography

Geography	Safety Population (N=183) n/N (%)	Effectiveness Population (N=100) n/N (%)
US	92/183 (50.3%)	73/100 (73%)
OUS	91/183(49.7%)	27/100 (27%)

Baseline Demographics & Medical History

Table 5 summarizes the baseline demographics and medical history of participants in the SOLVE-CRT Study. Overall, there were no significant differences in demographics or medical history between the Safety and Effectiveness populations.

The mean age in the Safety population was 68.1 ± 10.28 years and 68.2 ± 10.47 years in the Effectiveness population, with 66.7% and 67.0% over 65 years of age, respectively. Most patients were male (77.0% in the Safety population and 76.0% in the Effectiveness population) and white (85.8% in the Safety population and 82.0% in the Effectiveness population).

Most had NYHA class III symptoms (65.4% Safety, 65.0% Effectiveness). In addition, about half of the participants in each population had a history of atrial tachyarrhythmia and non-ischemic cardiomyopathy, and about one-third in each population had a history of ventricular tachyarrhythmia. Study participants in both populations had histories of coronary artery disease, cerebrovascular disease, renal dysfunction, pulmonary disorder, or other medical conditions. These characteristics of the study population are consistent with advanced HF with multiple comorbidities and a poor prognosis.

Table 5. Baseline Demographics and Medical History

Variable	Safety Population(N=183)	Effectiveness Population(N=100)
	Mean ± SD (N) (Min-Max) or n/N (%)	Mean ± SD (N) (Min-Max) or n/N (%)
Age (Years)	68.1 ± 10.28 (183) (32 – 88)	68.2 ± 10.47 (100) (36 – 88)
Age ≥ 65 Years	122/183 (66.7%)	67/100 (67.0%)
Male	141/183 (77.0%)	76/100 (76.0%)
Body Mass Index (BMI) (kg/m2)	30.8 ± 5.75 (183) (19 – 51)	30.6 ± 5.45 (100) (19 – 50)
Systolic Blood Pressure (SBP) (mmHg)	119.2 ± 18.69 (183) (79 – 200)	117.5 ± 17.68 (100) (79 – 180)
Diastolic Blood Pressure (DBP) (mmHg)	70.3 ± 10.58 (183) (44 – 100)	69.5 ± 10.45 (100) (44 – 94)
Heart Rate (HR) (bpm)	70.0 ± 10.59 (183) (50 – 100)	70.4 ± 10.25 (100) (50 – 100)
Ethnicity		
Hispanic	7/183 (3.8%)	6/100 (6.0%)
Not Hispanic	170/183 (92.9%)	94/100 (94.0%)
Choose not to answer	6/183 (3.3%)	0/100 (0.0%)
Race		
American Indian or Alaska Native	1/183 (0.5%)	1/100 (1.0%)
Asian	2/183 (1.1%)	2/100 (2.0%)
Black	12/183 (6.6%)	10/100 (10.0%)
Native Hawaiian or Other Pacific Islander	1/183 (0.5%)	1/100 (1.0%)
White	157/183 (85.8%)	82/100 (82.0%)
Chose not to answer	10/183 (5.5%)	4/100 (4.0%)
NYHA		
Class I	0/182 (0.0%)	0/100 (0.0%)
Class II	63/182 (34.6%)	35/100 (35.0%)
Class III	119/182 (65.4%)	65/100 (65.0%)
Class IV	0/182 (0.0%)	0/100 (0.0%)
Rhythm Disorders		

Variable	Safety Population(N=183)	Effectiveness Population(N=100)
	Mean ± SD (N) (Min-Max) or n/N (%)	Mean ± SD (N) (Min-Max) or n/N (%)
History of atrial tachyarrhythmia	*92/183 (50.3%)*	*52/100 (52.0%)*
Supraventricular tachycardia	74/183 (40.4%)	46/100 (46.0%)
Atrial fibrillation	19/183 (10.4%)	5/100 (5.0%)
Persistent	3/183 (1.6%)	1/100 (1.0%)
Permanent	0/183 (0.0%)	0/100 (0.0%)
Paroxysmal	16/183 (8.7%)	4/100 (4.0%)
Prior cardioversion	6/183 (3.3%)	1/100 (1.0%)
Atrial flutter	8/183 (4.4%)	2/100 (2.0%)
History of ventricular tachyarrhythmia	*67/183 (36.6%)*	*34/100 (34.0%)*
Ventricular tachycardia	61/183 (33.3%)	31/100 (31.0%)
Ventricular fibrillation	18/183 (9.8%)	7/100 (7.0%)
Type of Cardiomyopathy		
Non-ischemic cardiomyopathy	94/183 (51.4%)	50/100 (50.0%)
Ischemic cardiomyopathy	87/183 (47.5%)	50/100 (50.0%)
Non-ischemic + ischemic cardiomyopathy	2/183 (1.1%)	0/100 (0.0%)
Associated Conditions/ Prior Surgeries		
Prior cardiac device implant	*183/183 (100.0%)*	*100/100 (100.0%)*
Pacemaker	28/183 (15.3%)	21/100 (21.0%)
ICD	69/183 (37.7%)	48/100 (48.0%)
CRT-P	11/183 (6.0%)	4/100 (4.0%)
CRT-D	124/183 (67.8%)	59/100 (59.0%)
LV lead	109/183 (59.6%)	51/100 (51.0%)
Other	18/183 (9.8%)	16/100 (16.0%)
Coronary artery disease history	*104/183 (56.8%)*	*60/100 (60.0%)*
Prior MI	74/183 (40.4%)	41/100 (41.0%)
Prior PTCA	55/183 (30.1%)	30/100 (30.0%)
Prior CABG	53/183 (29.0%)	30/100 (30.0%)
Unstable angina	6/183 (3.3%)	2/100 (2.0%)
Cardiac valve surgical history	*19/183 (10.4%)*	*14/100 (14.0%)*
Aortic valve replacement	8/183 (4.4%)	6/100 (6.0%)
Mitral valve repair or replacement	10/183 (5.5%)	7/100 (7.0%)
Other valve replacement	5/183 (2.7%)	5/100 (5.0%)
Cerebrovascular disease history	*28/183 (15.3%)*	*16/100 (16.0%)*
Prior stroke/ CVA	19/183 (10.4%)	11/100 (11.0%)
Prior TIA	10/183 (5.5%)	6/100 (6.0%)
Renal dysfunction history	*51/183 (27.9%)*	*31/100 (31.0%)*

Variable	Safety Population(N=183)	Effectiveness Population(N=100)
	Mean ± SD (N) (Min-Max) or n/N (%)	Mean ± SD (N) (Min-Max) or n/N (%)
eGFR	64.3 ± 22.20 (174) (25 – 146)	64.3 ± 21.95 (94) (29 – 146)
Pulmonary disorder history	*65/183 (35.5%)*	*38/100 (38.0%)*
Chronic obstructive pulmonary disease	25/183 (13.7%)	11/100 (11.0%)
Current smoker	6/183 (3.3%)	4/100 (4.0%)
Former smoker	56/183 (30.6%)	33/100 (33.0%)
Other conditions	*138/183 (75.4%)*	*74/100 (74.0%)*
Systemic hypertension	99/183 (54.1%)	63/100 (63.0%)
Diabetes	64/183 (35.0%)	31/100 (31.0%)
Insulin dependent	21/183 (11.5%)	8/100 (8.0%)
Non-insulin dependent	43/183 (23.5%)	23/100 (23.0%)
Dyslipidemia	94/183 (51.4%)	50/100 (50.0%)
Hyperthyroidism	5/183 (2.7%)	5/100 (5.0%)
Sleep apnea	43/183 (23.5%)	24/100 (24.0%)
Pulmonary artery hypertension	11/183 (6.0%)	3/100 (3.0%)
Peripheral vascular disease	16/183 (8.7%)	8/100 (8.0%)
Cancer	27/183 (14.8%)	15/100 (15.0%)

Baseline Endpoint Measurements

Baseline measurements for clinical variables used for primary safety and Effectiveness endpoints are presented in Table 6.

In the Safety population, mean LVESV was 151.1 ± 67.21 ml, mean LVEDV was 210.4 ± 77.8 ml, and mean LVEF was 29.8 ± 7.9%.

In the Effectiveness population, mean LVESV was 146.3 ± 71.5 ml, mean LVEDV was 206.8 ± 83.6 ml, and mean LVEF was 31.1 ± 7.9%. Mean intrinsic QRS, paced QRS, KCCQ score, NT-proBNP level, and APCT are also presented in Table 6**.**

The baseline endpoint measures were similar between the two study populations and describe a population of patients with advanced HF.

Table 6. Baseline Endpoint Measurements

Variable	Safety Population (N=183)	Effectiveness Population (N=100)
	Mean ± SD (N) Median (Min-Max) or n/N (%)	Mean ± SD (N) Median (Min-Max) or n/N (%)
Echocardiographic Parameters		

Variable	Safety Population (N=183)	Effectiveness Population (N=100)
	Mean ± SD (N) Median (Min-Max) or n/N (%)	Mean ± SD (N) Median (Min-Max) or n/N (%)
LVESV (ml)	151.1 ± 67.21 (181) 138.0 (31 – 409)	146.3 ± 71.51 (100) 125.5 (31 – 409)
LVEDV (ml)	210.4 ± 77.76 (181) 195.0 (49 – 476)	206.8 ± 83.58 (100) 185.5 (49 – 476)
LVEF (%)	29.8 ± 7.90 (181) 30.1 (9 – 56)	31.1 ± 7.89 (100) 31.0 (14 – 56)
Other		
Intrinsic QRS (ms)	165.7 ± 21.69 (92) 162.0 (122 – 231)	166.1 ± 21.10 (49) 162.0 (134 – 231)
Paced QRS (ms)	182.8 ± 26.59 (138) 179.3 (108 – 257)	184.9 ± 24.72 (82) 182.0 (131 – 246)
KCCQ overall summary score	54.7 ± 22.90 (182) 56.0 (3 – 100)	57.2 ± 21.38 (100) 59.8 (13 – 94)
NT-proBNP (pg/ml)	1626.2 ± 2172.41 (153) 882.0 (49 – 14974)	1761.6 ± 2463.09 (86) 1039.5 (49 – 14974)
Acoustic pacing capture threshold (APCT) (mJ)	0.5 ± 0.86 (110) 0.2 (0 – 6)	0.5 ± 0.57 (87) 0.3 (0 – 3)

Baseline Heart Medications

Table 7 provides details of background medical therapy. Overall, these results reflect contemporary medication usage trends and show that the study population was medically optimized for HF treatment prior to entry into the trial.

Table 7. Baseline Heart Medications for Participants

Medication Type	Safety Population (N=183) n/N (%)	Effectiveness Population (N=100) n/N (%)
ACE or ARB or ARNI	168/183 (91.8%)	93/100 (93.0%)
Angiotensin-converting enzyme (ACE) inhibitor	59/183 (32.2%)	30/100 (30.0%)
Angiotensin receptor blocker (ARB)	74/183 (40.4%)	38/100 (38.0%)
Angiotensin receptor-neprilysin inhibitor (ARNI)	68/183 (37.2%)	44/100 (44.0%)
Beta-Blocker	174/183 (95.1%)	94/100 (94.0%)
Aldosterone Antagonist	115/183 (62.8%)	58/100 (58.0%)

Medication Type	Safety Population (N=183) n/N (%)	Effectiveness Population (N=100) n/N (%)
Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor	6/183 (3.3%)	6/100 (6.0%)
Diuretic	145/183 (79.2%)	81/100 (81.0%)
Digitalis	11/183 (6.0%)	6/100 (6.0%)
I_f Channel Inhibitor	4/183 (2.2%)	3/100 (3.0%)
Nitrate	37/183 (20.2%)	20/100 (20.0%)

D. Safety and Effectiveness Results

1. Primary Safety Results

The safety analysis was based on all 108 participants from Part II Randomized and 75 participants from Part III Single-Arm of the Study for a total of 183 patients. The key safety outcomes for this study are presented in Table 8 to Table 11.

Adverse effects are reported in Table 10 and Table 11.

In the Safety population, there was an 80.9% rate (148/183 patients) of freedom from Type I complications with a lower bound of the one-sided 98.8% confidence interval of 73.4%, above the 70% performance goal ($p < 0.001$). Thus, the primary safety endpoint was achieved.

Further, a Kaplan-Meier sensitivity analysis was conducted, showing a freedom from Type I complications of 80.6%, with a lower confidence bound of 72.8%, above the performance goal of 70% which confirmed the success of the primary safety endpoint.

Table 8. Freedom from Type I Complication Rate through 6 Months (Safety Population)

Freedom from Type I Complication Rate (N=183)	Analysis Time Point	LCB*	Performance Goal	Study Endpoint Conclusion
80.9%	Interim	73.4%	70%	**MET** ***p < 0.001***

*LCB: Primary safety interim analysis used one-sided alpha of 0.012 equivalent to two-sided alpha of 0.024

Table 9. Kaplan-Meier Analysis for Freedom from Type I Complication Rate Estimate at 6 Months.

Freedom from Type I Complications Kaplan-Meier Rate Estimate (N=183)	LCB	Performance Goal
80.6%	72.8%	70%

Adverse Effects that occurred in the study

Adverse events reported from baseline to six months post implant were adjudicated by the CEC. The key safety outcomes for this study are presented in Table 10. Both observations and complications were reported.

An observation was defined as an AE that does not result in invasive intervention or could be corrected by simple adjustments.

A complication was defined as an AE that resulted in injury, or significant or permanent disability and fulfilled any one or more of the following:

1. An event that cannot be treated or resolved by simple adjustments/ treatments and requires invasive intervention, intravenous medication, blood product administration, hospitalization or re-hospitalization after discharge, or prolonged hospitalization (> 48 hours) prior to discharge, or any combination thereof
2. A procedure- or device-related pericardial effusion or pseudoaneurysm resulting in a procedure
3. An event that results in significant or permanent loss of device function
4. An event that results in death

Complications were further defined by Type I, II, III, or IV.

Type I complications were those that were caused by a component of the study device system (the WiSE CRT System Transmitter, Battery, Electrode, Catheter, Sheath, and/or Programming Software), or specific procedure-related events including vascular events, stroke, pericardial effusion, and pocket events. Note that failure to implant or a failed implant attempt did not count as a Type I complication unless it was associated with an event that was classified as such.

Type II complications were other procedure-related events not specifically caused by a component of the study device system, but that would not have occurred in the absence of the study implantation procedure.

Type III complications were events that were caused by a change in the participant's condition unrelated to the implanted study device system or the implantation procedure.

Type IV complications were pre-existing medical conditions or conditions that occurred while the participant was not enrolled in the Study.

Table 10 shows CEC-adjudicated AEs that occurred through six months post implant in the Safety population of the SOLVE-CRT Study. There were no

unanticipated adverse device effects (UADEs).
Overall, 177 complications occurred in 86 of 183 participants in the Safety population (47.0%). Of the 86 participants who experienced a complication, 19.1% (35/183) had a Type I, 7.7% (14/183) had a Type II, 12.6% (23/183) had a Type III, and 25.7% (47/183) had a Type IV complication.
Of the 35 participants who experienced a Type I complication, 6.6% had a study device system event, 2.7% had a vascular event, 1.6% had a stroke or other thromboembolic event, 3.8% had a cardiac perforation, and 6.6% had a pocket event. Four (4) cardiac perforations required surgical intervention and three (3) were treated with pericardiocentesis of which two (2) appeared to be related to the transseptal puncture. The cardiac perforations requiring surgical intervention occurred early in the study and prompted some additional safety measures for the implant, including the use of real time echocardiography during the Electrode implant. No LV perforations requiring surgical intervention were observed after the implementation of this mitigation.
In addition, the CEC adjudicated 169 observations in 82 of the 183 participants (44.8%) in the Safety population.

Table 10. Adjudicated AEs with ≤ 6 Months Post Procedure

Adjudicated Adverse Events Categorization	Safety Population (N=183) N Patients (% Patients) [N Events]
No Complications of Any Type, N Patients (% Patients)	97 (53.0%)
Complications	***86 (47.0%) [177]***
Type I or II	43 (23.5%) [67]
Type I	***35 (19.1%) [43]***
Study device system event	12 (6.6%) [12]
Vascular event (not caused by closure device)	5 (2.7%) [5]
Stroke and other thromboembolic events (e.g., TIA)	3 (1.6%) [3]
Cardiac perforation	7 (3.8%) [7]
Surgically repaired	4 (2.2%) [4]
Pericardiocentesis	3 (1.6%) [3]
Pocket events	12 (6.6%) [15]
Other	1 (0.5%) [1]
Type II	14 (7.7%) [24]
Type III	23 (12.6%) [32]
Type IV	47 (25.7%) [78]
Observations	82 (44.8%) [169]
UADEs	0 (0%) [0]

Type I Complications by Category

Table 11 provides an overview of Type I complications through six months by CEC-adjudicated category and site reported AE terms. Overall, 35 of 183 participants in the Safety population experienced 43 Type I complications for a rate of 19.1% (13.7%, 25.6%).

Twelve participants (6.6%; 3.4%, 11.2%) experienced a study device system event, including two (2) device migrations, two (2) failures to capture, one (1) device dislocation, one (1) ventricular tachyarrhythmias, one (1) medical device replacement, one (1) device component issue, two (2) device dislodgements, and two (2) device embolizations.

Five (5) participants (2.7%; 0.9%, 6.3%) had vascular events including one (1) retroperitoneal hematoma, one (1) leg ischemia, two (2) groin hematomas, one (1) iliac artery perforation.

There were also three (3) participants (1.6%; 0.3%, 4.7%) who experienced a stroke or other thromboembolic event.

Further 12 participants (6.6%; 3.4%, 11.2%) experienced a pocket event, including one (1) fatigue, four (4) hematomas, one (1) pneumothorax, one (1) wound dehiscence, one (1) wound infection, one (1) implant site erosion, one (1) implant site hematoma, one (1) incision site infection, one (1) acute anemia (one (1) device issue, and one (1) implant site pocket infection.

Finally, there were seven (7) participants (3.8%; 1.6%, 7.7%) with cardiac

perforations, including three (3) with cardiac tamponade, two (2) with pericardial effusion, one (1) cardiac perforation, and one (1) pulseless electrical activity.

Table 11. Type I Complications through 6 Months by Category

Categorization	Safety Population (N=183) N Patients, (% Patients) [N Events], LCB, UCB
Study Device System Event	***12 (6.6%) [12], 3.4%, 11.2%***
Device migration	2 (1.1%) [2], 0.1%, 3.9%
Failure to capture	2 (1.1%) [2], 0.1%, 3.9%
Device dislocation	1 (0.5%) [1], 0.0%, 3.0%
Ventricular tachyarrhythmia	1 (0.5%) [1], 0.0%, 3.0%
Medical device replacement	1 (0.5%) [1], 0.0%, 3.0%
Device component issue	1 (0.5%) [1], 0.0%, 3.0%
Device dislodgement	2 (1.1%) [2], 0.1%, 3.9%
Device embolization	2 (1.1%) [2], 0.1%, 3.9%
Vascular Event (not caused by closure device)	***5 (2.7%) [5], 0.9%, 6.3%***
Retroperitoneal hematoma	1 (0.5%) [1], 0.0%, 3.0%
Leg ischemia	1 (0.5%) [1], 0.0%, 3.0%
Groin hematoma	2 (1.1%) [2], 0.1%, 3.9%
Iliac artery perforation	1 (0.5%) [1], 0.0%, 3.0%
Stroke and Other Thromboembolic Events (e.g., TIA)	***3 (1.6%) [3], 0.3%, 4.7%***
Cerebrovascular accident	1 (0.5%) [1], 0.0%, 3.0%
Stroke	1 (0.5%) [1], 0.0%, 3.0%
Ischemic stroke	1 (0.5%) [1], 0.0%, 3.0%
Cardiac Perforation	***7 (3.8%) [7], 1.6%, 7.7%***
Cardiac tamponade	3 (1.6%) [3], 0.3%, 4.7%
Pericardial effusion	2 (1.1%) [2], 0.1%, 3.9%
Cardiac perforation	1 (0.5%) [1], 0.0%, 3.0%
Pulseless electrical activity	1 (0.5%) [1], 0.0%, 3.0%
Pocket Event	***12 (6.6%) [15], 3.4%, 11.2%***
Fatigue	1 (0.5%) [1], 0.0%, 3.0%
Hematoma	4 (2.2%) [4], 0.6%, 5.5%
Pneumothorax	1 (0.5%) [1], 0.0%, 3.0%
Wound dehiscence	2 (1.1%) [2], 0.1%, 3.9%
Wound infection	1 (0.5%) [1], 0.0%, 3.0%
Implant site erosion	1 (0.5%) [1], 0.0%, 3.0%
Implant site hematoma	1 (0.5%) [1], 0.0%, 3.0%
Incision site infection	1 (0.5%) [1], 0.0%, 3.0%
Acute anemia	1 (0.5%) [1], 0.0%, 3.0%
Device issue	1 (0.5%) [1], 0.0%, 3.0%
Implant site pocket infection	1 (0.5%) [1], 0.0%, 3.0%
Other	***1 (0.5%) [1], 0.0%, 3.0%***

Categorization	Safety Population (N=183)
	N Patients, (% Patients) [N Events], LCB, UCB
Anemia postoperative	1 (0.5%) [1], 0.0%, 3.0%
Total	**35 (19.1%) [43], 13.7%, 25.6%**

2. Primary Effectiveness Results

The Effectiveness analysis was based on a total of 100 participants at six months post implant, 25 PU-HRU Part II participants randomized to the Treatment arm and 75 PU-HRU Part III Single-Arm participants at the 6-month time point. Key effectiveness outcomes are presented in Table 12. The primary Effectiveness endpoint for the SOLVE-CRT Study was the mean relative (%) change in LVESV from baseline to six months compared to a performance goal of -9.3%.

Table 12 shows the absolute and relative changes in LVESV at six months post implant in comparison to baseline using imputed data. With imputation, measurements of LVESV were available at baseline and six months for 92 of 100 participants (92.0%) in the Effectiveness population. The mean relative change in LVESV among those participants was -16.4 ± 22.5% (95% CI, -21.0% to -11.7%) with an upper confidence bound below the -9.3% performance goal ($p = 0.003$), meeting the primary Effectiveness endpoint. The absolute change in LVESV was -22.8 ± 36.2 ml (95% CI: --30.3, --15.3) which was also statistically significant ($p < 0.001$).

Table 12. Relative and Absolute Change in LVESV at 6 Months from Baseline (Imputed*)

Characteristic	Effectiveness Population‡ (N=100)	95% CI	Study Endpoint Conclusion
Baseline (ml)			
N	100	-----	-----
Mean	146.3	132.1, 160.5	-----
SD	71.51	-----	-----
Median (IQR)	125.5 (95.0, 170.5)	-----	-----
Min, Max	31.0, 409.0	-----	-----
Six Months (ml)			
N	92	-----	-----
Mean	125.4	109.3, 141.5	-----
SD	77.67	-----	-----
Median (IQR)	97.5 (75.0, 158.0)	-----	-----
Min, Max	30.0, 368.4	-----	-----
Absolute Change from Baseline at Six Months (ml)			
N	92	-----	-----

Characteristic	Effectiveness Population‡ (N=100)	95% CI	Study Endpoint Conclusion
Mean	-22.8	-30.3, -15.3	-----
SD	36.22	-----	-----
Median (IQR)	-21.0 (-49.5, 0.0)	-----	-----
Min, Max	-123.0, 67.4	-----	-----
Relative Change from Baseline at Six Months (%)			
N	92	-----	-----
Mean	-16.4	-21.0, -11.7	MET (***p = 0.003***)
SD	22.50	-----	-----
Median (IQR)	-15.4 (-34.2, 0.0)	-----	-----
Min, Max	-64.1, 36.1	-----	-----

‡Effectiveness population = 100 subjects consisting of all Previously Untreatable (PU) and High-risk Upgrade (HRU) Part II subjects randomized to Treatment and up to first 75 subjects enrolled in Part III.

*Imputation groups were established based on the following baseline characteristics: indication for CRT (PU or HRU), sex, age group (≥65 vs. < 65) and baseline LVESV quartile. The worst-case relative change (%) in LVESV from the matching imputation group for subjects with missing not at random (MNAR) data was used as the imputed datapoint.

The primary Effectiveness endpoint was also evaluated in the As Treated and Per Protocol analysis populations, and results were similar to the Effectiveness population; namely, the primary Effectiveness endpoint was met in both of these analysis populations.

Data Poolability

Data Poolability was tested for the primary safety endpoint and the primary Effectiveness endpoint by three poolability factors: 1) Study Part (Randomized vs Single-Arm), 2) Geography (US, EU, UK, AU), and 3) Study Site. Both primary endpoints passed ($p > 0.05$) poolability testing across all three factors.
Since both the primary Effectiveness and safety endpoints met the pre-specified stopping rules for interim analysis, the trial was concluded as a success.

Secondary Effectiveness Results

Secondary Effectiveness endpoints were not formally tested. Proportion of participants or descriptive statistics are summarized.

Key secondary Effectiveness outcomes are presented in **Table** 13 to **Table** 17 below. Secondary endpoints included KCCQ responders, percent BiV pacing, left ventricular ejection fraction (LVEF) responders, and acoustic pacing capture threshold (APCT).

KCCQ Score

Among the 87 participants with KCCQ scores, 57 (65.5%) had an absolute increase of ≥ 5 points in their KCCQ score.

Table 13: KCCQ Responders from Pre-Implant to 6 months - by Analysis Population

	Proportion of subjects achieving an increase in KCCQ Overall Summary Score of 5 points or greater from pre-implant to 6 months
Analysis Population	**n/N (%)**
Effectiveness Population	57/87 (65.5%)
Per Protocol	57/87 (65.5%)
As Treated	57/87 (65.5%)

Percent Biventricular Pacing

Among the 86 participants with BiV pacing data, the mean percent BiV pacing was 93.1 ± 13.0%. These results indicate the WiSE CRT System was able to deliver effective BiV pacing for CRT > 93% of the time in those participants.

Table 14: Mean % Bi-ventricular Pacing at 6 Months - by Analysis Population

	% Bi-ventricular Pacing at 6 Months
Analysis Population	**Mean ± SD (N)**
Effectiveness Population	93.1 ± 12.96 (86)
Per Protocol	93.1 ± 12.96 (86)
As Treated	93.1 ± 12.96 (86)

LVEF Responders

Among the 89 participants with available data, 41 (46.1%) had an absolute increase in LVEF ≥ 5%.

Table 15: LVEF Responders from Pre-Implant to 6 months - by Analysis Population

	Proportion of subjects achieving an increase in LVEF of 5% or greater from pre-implant to 6 months
Analysis Population	**(N=100)**
	n/N (%)
Effectiveness Population	41/89 (46.1%)
Per Protocol	41/89 (46.1%)
As Treated	41/89 (46.1%)

APCT

The acoustic pacing capture threshold is a measure of the energy needed to deliver a pacing pulse at the capture threshold. Among the 83 participants with available data, 79 (95.2%) achieved an APCT of < 2.9 mJ indicating that in greater than 95% of participants, the WiSE CRT System could be programmed as intended to deliver BiV pacing for CRT.

Table 16: Proportion of Patients with APCT less than 2.9 mJ at 6 months

	Proportion of subjects with APCT less than 2.9 mJ
Analysis Population	**n/N (%)**
Effectiveness Population	79/83 (95.2%)
Per Protocol	79/83 (95.2%)
As Treated	79/83 (95.2%)

APCT Stability

Among 75 participants with available data, 61 (81.3%) had a relative increase in APCT from pre-discharge to six months that was less than 3x, characterizing the stability of energy usage to maintain pacing through this period.

Table 17: Proportion of patients whose APCT relative increase from pre-discharge to 6 months is less than 3x by Analysis Population

	Proportion of patients whose APCT relative increase from pre-discharge to 6 months is less than 3x
Analysis Population	**n/N (%)**
Effectiveness Population	61/75 (81.3%)
Per Protocol	61/75 (81.3%)
As Treated	61/75 (81.3%)

3. Subgroup Analyses

a) Freedom from Type I Complications

A subgroup analysis for freedom from Type I complications through six months in the Safety population was conducted (Table 13). Due to small sample size only descriptive statistics are provided.

Table 18. Subgroup Analysis of Freedom from Type I Complication Rate through 6 Months (Safety Population)

Variable	Subgroup	N	Freedom from Type I Complication Rate (%)
Overall	Safety population	183	148/183 (80.9%)
Sex	Male	141	119/141 (84.4%)
	Female	42	29/42 (69.0%)
Race	White	157	125/157 (79.6%)
	Black	12	11/12 (91.7%)
	Other	4	4/4 (100.0%)
	Chose not to answer	10	8/10 (80.0%)
Age	≥ 65 years	122	98/122 (80.3%)
	< 65 years	61	50/61 (82.0%)
NYHA Class	Class II	63	51/63 (81.0%)
	Class III/IV	119	96/119 (80.7%)
LVESV at Baseline	≥ 150 mL	79	65/79 (82.3%)
	< 150 mL	102	81/102 (79.4%)
LVEDV at Baseline	≥ 200 mL	87	72/87 (82.8%)
	< 200 mL	94	74/94 (78.7%)
LVEF at Baseline	≥ 30%	97	76/97 (78.4%)
	< 30%	84	70/84 (83.3%)
Peripheral Artery Disease	Yes	16	12/16 (75.0%)
	No	167	136/167 (81.4%)
Chronic Obstructive Pulmonary Disorder	Yes	25	19/25 (76.0%)
	No	158	129/158 (81.6%)
Renal Dysfunction	Yes	51	37/51 (72.5%)
	No	132	111/132 (84.1%)
Atrial Fibrillation	Yes	19	12/19 (63.2%)
	No	164	136/164 (82.9%)
Diabetes	Yes	64	49/64 (76.6%)
	No	119	99/119 (83.2%)
Cancer	Yes	27	21/27 (77.8%)

Variable	Subgroup	N	Freedom from Type I Complication Rate (%)
	No	156	127/156 (81.4%)
Cardiac Valve Surgery	Yes	19	18/19 (94.7%)
	No	164	130/164 (79.3%)
Progression of HF	Device ≥ 3 years	102	85/102 (83.3%)
	Device < 3 years	81	63/81 (77.8%)
Co-Implant	CRT	122	98/122 (80.3%)
	ICD	42	34/42 (81.0%)
	IPG	15	12/15 (80.0%)
Eligibility for SOLVE-CRT	Previously untreatable	110	89/110 (80.9%)
	High risk upgrade	29	23/29 (79.3%)
	Non-responder	44	36/44 (81.8%)
Cardiomyopathy	Ischemic	87	72/87 (82.8%)
	Non-ischemic	94	74/94 (78.7%)
ACE	Yes	59	47/59 (79.7%)
	No	124	101/124 (81.5%)
ARB	Yes	74	63/74 (85.1%)
	No	109	85/109 (78.0%)
ARNI	Yes	68	57/68 (83.8%)
	No	115	91/115 (79.1%)
Beta-Blocker	Yes	174	141/174 (81.0%)
	No	9	7/9 (77.8%)
Mineralocorticoid Receptor Antagonist	Yes	115	97/115 (84.3%)
	No	68	51/68 (75.0%)
SGLT2 Inhibitor	Yes	6	5/6 (83.3%)
	No	177	143/177 (80.8%)
$CHADS_2$ Score	≥ 3	90	68/90 (75.6%)
	< 3	93	80/93 (86.0%)

b) Relative Change in LVESV

A subgroup analysis for relative change in LVESV was conducted (Table 14). Due to small sample size only descriptive statistics are provided:

Table 19. Subgroup Analysis of Relative change in LVESV at 6 Months from Baseline

Variable	Subgroup	N	Mean relative change in LVESV at 6 Months from Baseline
Overall	Effectiveness Population	89	-17.7
Sex	Male	68	-17.0
	Female	21	-20.0
Race	White	72	-21.0
	Black	9	-6.6
	Other	4	6.7
	Chose not to answer	4	-7.7
Age	≥ 65 years	56	-18.9
	< 65 years	33	-15.6
NYHA	Class II	33	-16.9
	Class III/IV	56	-18.1
LVESV at Baseline	≥ 150 ml	34	-15.3
	< 150 ml	55	-19.2
LVEDV at Baseline	≥ 200 ml	39	-18.9
	< 200 ml	50	-16.7
LVEF at Baseline	≥ 30%	49	-21.6
	< 30%	40	-12.9
Peripheral Artery Disease	Yes	7	-11.2
	No	82	-18.2
Chronic Obstructive Pulmonary Disorder	Yes	10	-2.6
	No	79	-19.6
Renal dysfunction	Yes	27	-14.8
	No	62	-18.9
Atrial fibrillation	Yes	5	-26.0
	No	84	-17.2
Diabetes	Yes	27	-9.6
	No	62	-21.2

Variable	Subgroup	N	Mean relative change in LVESV at 6 Months from Baseline
Cancer	Yes	15	-26.4
	No	74	-15.9
Cardiac Valve Surgery	Yes	13	-24.3
	No	76	-16.5
Progression of Heart Failure	Device ≥ 3 years	44	-13.6
	Device < 3 years	45	-21.7
Co-Implant	CRT	48	-17.0
	ICD	32	-18.7
	IPG	9	-17.6
Eligibility for SOLVE-CRT	Previously Untreatable	66	-16.6
	High Risk Upgrade	23	-20.9
Cardiomyopathy	Ischemic	45	-12.9
	Non-ischemic	44	-22.6
ACE	Yes	26	-10.2
	No	63	-20.8
ARB	Yes	34	-19.3
	No	55	-16.7
ARNI	Yes	40	-20.2
	No	49	-15.6
Beta-Blocker	Yes	84	-17.5
	No	5	-21.3
Mineralocorticoid Receptor Antagonist	Yes	51	-16.8
	No	38	-18.9
SGLT2 Inhibitor	Yes	5	1.1
	No	84	-18.8

4. **Pediatric Extrapolation**
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included

68 investigators. None of the clinical investigators had disclosable financial interests arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The clinical study included several ancillary endpoints were analyzed from baseline to six months post implant in the Effectiveness population without formal pre-specified hypothesis tests. This included echocardiographic parameters, NT-proBNP, QRS, and NYHA class. See the discussion above under Secondary Effectiveness Results.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

At 6-month post implant, the primary Effectiveness endpoint was met with a 16.4% (95% CI: 11.7% to 21.0%) reduction in mean LVESV, which was statistically significant compared to the -9.3% performance goal ($p = 0.003$).
Secondary Effectiveness endpoints included an APCT of < 2.9 mJ achieved in 95.2% of participants, while 81.3% participants had a relative increase in APCT from pre-discharge to six months that was less than 3x. The mean percent BiV pacing of 93.1%, an increase in LVEF ≥ 5% in 46.1% of participants, and ≥ 5 points increase in KCCQ in 65.5% of participants.

B. Safety Conclusions

The risks of the device are based on animal studies as well as data collected in the SOLVE-CRT Clinical Study conducted to support PMA approval as described above. In the Clinical Study, the freedom from procedure-or device-related (Type I) complications at 6-month post implant was 80.9% (lower boundary of the one-sided 98.8% CI, 73.4%) exceeding the pre-specified performance goal of 70% ($p<0.001$).

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The procedural success of the Study was 97.1%, and the WiSE CRT System delivered CRT to patients at a mean percent BiV pacing of 93.1%.

The primary Effectiveness endpoint of the Study was the relative mean percent change in LVESV. Among the Effectiveness population, the relative mean percent change reduction in LVESV was 16.4% which was statistically significant in comparison to the

performance goal of 9.3%. Device benefits included improvement in symptoms, heart function, and quality of life through six months post implant. It is important to note that these benefits occurred in patients who were already treated with HF medications following GDMT governed by an independent Eligibility Review Committee.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. All adverse events were adjudicated by an independent Clinical Events Committee. The primary safety endpoint, freedom from Type I (device- and procedure-related events) complications through six months post implant, was 80.9% which was statistically significant in comparison to the performance goal of 70%. The types of events and event rates reported for the WiSE CRT System were similar to those seen with conventional CRT and established alternatives. There were no chronic safety issues related to the use of ultrasound energy, and there were no unanticipated adverse device effects.

Additional factors to be considered in determining probable risks and benefits for the WiSE CRT System device includes the following:

- The SOLVE-CRT Study was revised to include a Single-Arm Part in which the responses were compared to an objective performance goal.
- There are some technological challenges during the implant procedure and the Battery and Transmitter are extra-thoracic requiring two separate chest wall incisions.

D. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

E. Overall Conclusions

The data in this application support the reasonable assurance of safety and Effectiveness of this device when used in accordance with the indications for use.

The prospective SOLVE-CRT study prospectively was conducted to demonstrate the safety and Effectiveness of the WiSE CRT System. The study met the pre-specified performance goals for both the safety (acceptable freedom from Type I complications through 6 months) and effectiveness (clinically-significant relative (%) change in LVESV from baseline to six months) endpoints.

The totality of evidence support a reasonable assurance that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIV. CDRH DECISION

CDRH issued an approval order on April 11, 2025. The final clinical conditions of approval cited in the approval order are described below.

The WiSE CRT System Post-Approval Study (PAS) is a prospective, real-world, observational study aimed at understanding acute and long-term product performance including patient safety, clinical outcomes, and CRT response information associated with the use of the market-released WiSE system. As per protocol synopsis received March 24, 2025, the goal is to enroll approximately 320 patients such that 250 implanted patients reach the 12 months follow up. Participants will be enrolled, implanted, and followed at one month, six months, and annually thereafter for the duration of the study through 5 years follow-up.
The primary endpoint is the rate of serious adverse events (SAEs) at ≤ 30 days post implant related to the WiSE CRT System and/or implant procedure.
The study will also measure:

1. Procedural Success
2. CRT Response Assessment
3. HF Clinical Composite Score
4. NYHA Classification
5. QRS Duration
6. 6 Minute Walk Test (6MWT)
7. Events Assessment
8. Mortality
9. Patient Global Assessment
10. Device Longevity and Battery Performance

Interim analyses will be conducted throughout the study. These analyses will be conducted for reporting purposes only without statistical inferences or intention to modify the study. The study sample size shall be based on the primary safety endpoint. All other endpoints will be reported.

Interim results and final results will be summarized and reported using descriptive statistics.

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number. In addition, the results from any surveillance should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.
From the date of study protocol approval, you must meet the following timelines for the WiSE CRT System PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of WiSE CRT System PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the PMA approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES (In Order of Mention)

Singh JP, Walsh MN, Kubo SH, et al. Modified design of stimulation of the left ventricular endocardium for cardiac resynchronization therapy in nonresponders, previously untreatable and high-risk upgrade patients (SOLVE-CRT) trial. Am Heart J 2021;235:158-162. (In eng). DOI: 10.1016/j.ahj.2021.02.008.

Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail 2017;23(8):628-651. DOI: 10.1016/j.cardfail.2017.04.014.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. Journal of the American College of Cardiology 2013;62(16):1495-1539. DOI: 10.1016/j.jacc.2013.05.020.