CardioMEMS™ HF System

Model CM3000

System Guide

ST. JUDE MEDICAL™

Do not attempt to use the device before reading and fully understanding the User's Manual and the System Guide.

Carefully inspect all product packaging for damage or defects prior to use.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

Contents

Description

The CardioMEMS HF System provides pulmonary artery (PA) hemodynamic data used for the monitoring and management of heart failure (HF) patients. The system measures changes in PA pressure which physicians use to initiate or modify heart failure treatment.

The system includes the following components:

- Implantable wireless sensor with delivery catheter
- Patient or Hospital Electronics System
- Patient database

The wireless sensor is designed for permanent implantation into the distal pulmonary artery. Once implanted, the CardioMEMS PA Sensor provides non-invasive hemodynamic data that is collected in the physician's office, clinic, hospital, or patient's home. The data provided by the system includes:

- PA pressure waveform
- Systolic, Diastolic, and Mean PA pressure
- Heart Rate

This hemodynamic data is transmitted to a secure website that serves as the patient database so that PA monitoring information is available at all times through the internet. Changes in PA pressure can be used in conjunction with heart failure signs and symptoms to guide adjustments to medications.

For information on the use of the sensor, please refer to the User's Manual. For information on the operation of the patient database, please refer to the Merlin.net™ Patient Care Network Heart Failure Management Application Help Manual. For clinical study information, please refer to the Clinical Study Information section.

Indications

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.

Contraindications

The CardioMEMS HF System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one month post implant.

Warnings

Before use of the system, read this guide.

- Only trained personnel should use this product.
- Avoid excessive or damaging force when using the Hospital Electronics System (Model # CM3000).
- Do not change the system configuration without authorization from the manufacturer.
- If two electronic units are proximate to each other and are used at the same time, pressure measurements may be affected due to interference between the two systems. In such isolated cases, it is recommended that operation of each electronics unit occur at separate times.
- Two hospital electronics systems may interfere with each other. Only operate one electronics unit at a time in the same general vicinity.
- The CM3000 requires special precautions regarding electromagnetic compatibility (EMC) and needs to be placed into service according to the EMC information provided. If interference is noted, remove or stop using the interfering equipment.
- The use of accessories, transducers and cables other than those specified, with the exception of transducers and cables sold by the manufacturer of the CM3000 as replacement parts for internal components, may result in increased emissions or decreased immunity of the CM3000. The use of other attachable parts other than the parts provided may result in inaccurate readings, damage to the system, or injury to the user.
- The CM3000 should not be used adjacent to or stacked with other equipment. If it is necessary to operate adjacent or stacked with other equipment, observe the CM3000 to verify normal operation in the configuration in which it will be used.
- Other equipment may interfere with the CM3000 operation, even if the other equipment complies with CISPR emission requirements. Refer to the EMI/EMC and Troubleshoot Procedure sections for guidance.
- There are minimum amplitudes for the CM3000 to measure physiological signals. Operation of the equipment below the minimum amplitudes may cause inaccurate results.
- Do not attempt to connect the Hospital Electronics System to any network or data coupling equipment in the hospital other than those specified.
- Follow instructions on shutting down equipment. Failure to do so may cause file corruption.
- While in use, ensure that the power supply is easily accessible since unplugging the device from the outlet is the only means of completely isolating from mains.
- Ingestion of any part of the system may cause injury.
- Care should be taken to keep all cables away from the neck and face to prevent airway blockage.
- Patients should be advised that if they develop redness of the skin or a change in skin sensitivity occurs, they should discontinue use of this product immediately and contact their physician.
- All sensors have a unique calibration. Ensure readings are only taken using the correct calibration information from the sensor. Use of the incorrect calibration information may result in an inaccurate reading.
- All right heart catheterizations must be performed under fluoroscopic guidance to prevent sensor dislodgement.
- The sensor is visible under plain film X-ray and fluoroscopy. Under CT imaging, there may be localized beam hardening artifact around sensor implant.

- This product is not made with natural rubber latex.

Precautions

- Store the CM3000 in a temperature controlled, clean and dry area.
- Use the CM3000 at temperatures between 5° to 40°C (41° to 104°F) and 15% to 93% humidity. Store the system between -25 to 70°C (-13° to 158°F) and up to 93% humidity.
- All electronic devices with the Hospital and Patient Electronics Systems, including components and accessories, are to be used only with the sensor and not with other products, appliances or devices. If there is evidence of a change in performance, please contact Technical Support to obtain more information.
- Avoid excessive or damaging force when using the AC adapter.
- Exposure to excess lint or dust may cause the system to malfunction.
- The system consists of an electronics unit and an antenna. If any of the following occurs, immediately unplug the electronics unit and contact Technical Support:
  - Any cords are noticeably frayed or damaged
  - Liquid has spilled onto the monitor, or it has been exposed to rain
  - The system has been dropped or the enclosure has been damaged
- If you lose the power cord, replace it with an identical cord. Contact Technical Support to obtain a new one.
- Only an authorized technician should remove the cover or attempt to service the device. The warranty may be voided otherwise.
- Do not place the system near a window. Exposing the LCD screen to rain, water, moisture or sunlight may severely damage it.
- Do not apply excessive pressure to the LCD screen. Excessive pressure may cause damage to the display.
- Portable and mobile RF communications equipment can affect medical electrical equipment and may cause a malfunction of the system.
- All new or refurbished equipment should be obtained from the manufacturer.
- The CM3000 may require secure data transfer through the use of the internet or networks. Portions of this internet or network pathway may become unavailable for periods of time for a variety of reasons including but not limited to: internet connectivity outage, hardware failure, power outage, or general infrastructure failures. Readings and data that are unable to transmit are stored and will transmit when connectivity is available.
- The mean pressure measurement accuracy of the system may be affected by various factors. Mean pressure measurement error has been observed when the sensor was deployed in a vessel which had an inner diameter of less than 7 mm, and in cases where there was an acute bend in the vessel of >30 degrees at the location of the sensor. Signs of mean pressure measurement error include the following:
  - Gradual mean pressure changes without a corresponding proportional change in the pulse pressure (systolic-diastolic pressure)
  - Negative mean pressures

  If either feature is observed, temporarily suspend use of the pressure information for management of the patient and contact Technical Support for further assistance. A right heart catheterization may be needed to recalibrate the Baseline (mean pressure) in order to continue use of the system.
- The touchscreen display on the handheld unit can be sensitive to electrostatic discharge (ESD) at high levels. To reduce the potential for ESD discharge to the touchscreen, remove and hold the plastic handle of the handheld prior to contact with the touchscreen.

  If the touchscreen becomes damaged due to ESD, the screen will be discolored or may be unresponsive. Contact Technical Support for replacement of the handheld unit.

  Please note that high levels of ESD are more likely in situations where the relative humidity is very low, such as inside a heated building during the winter in areas where it is cold outside. In order to reduce the potential for ESD levels, there are common situations which create static electricity that can be avoided prior to use, for example, putting on and removing clothes, dragging your feet across a carpet or rug, vacuuming, or removing clothes from a dryer.
- The system is not intended to be used in a severe electromagnetic radiation environment or an industrial environment.
- The system should not be used in conjunction or in association with Magnetic Resonance Imaging (MRI), computerized axial tomography (CT), diathermy, Radio Frequency Identification (RFID), and electromagnetic security systems such as metal detectors.

Package Contents

The system package contains:

- Hospital Electronics System
- Product documentation

Sterilization

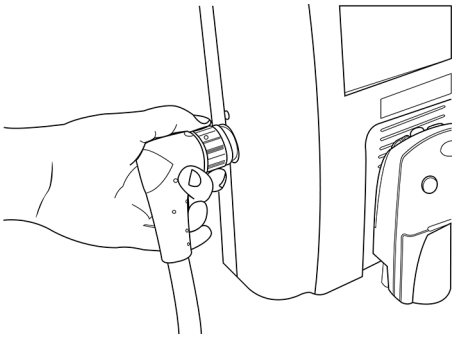
The Hospital Electronics System is provided non-sterile.

Components and Setup

Connect the System Cables

1. Align the keyed antenna at an approximately 30 degree angle and twist on the locking connector.

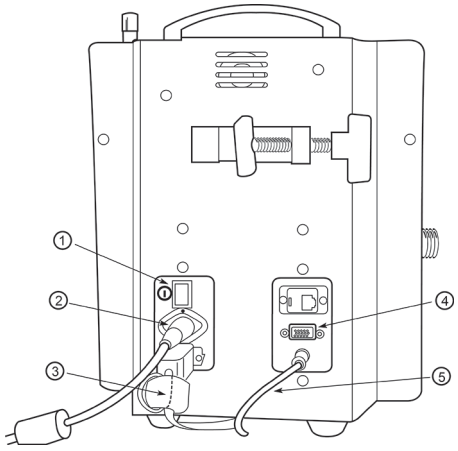
Figure 1. Connecting the antenna



2. Attach the connectors as shown in the figure below.
   Connectors:
   - Power supply connector (5 pin DIN)
   - Printer serial communication cable (9 pin D-SUB)
   - Printer power cable

   NOTE: A VGA cable can be connected to the auxiliary VGA connector.

Figure 2. The connectors



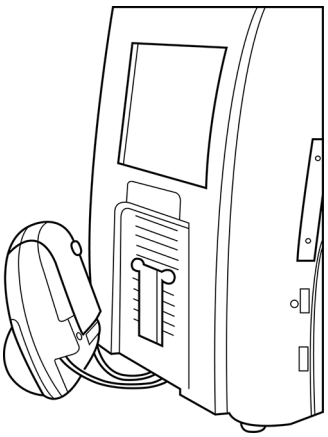
1. Power switch
2. Power cable
3. Printer serial cable
4. VGA connection
5. Printer power cable

3. Plug the power cord into the power supply and plug the power cord into the wall.

Printer

The printer clips into the mount on the front of the electronics unit. The cables for the printer run under the electronics unit. Disconnect them if necessary.

Figure 3. The printer mount

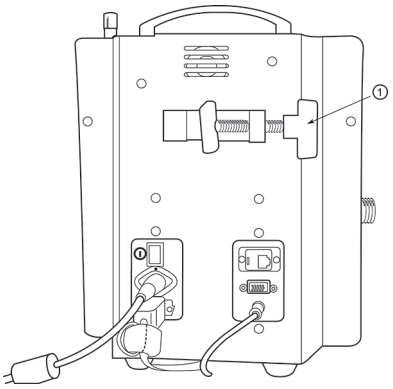


The Pole Attachment

1. To mount the electronics unit to a pole, use the pole clamp.
2. Ensure that the pole is sturdy and can remain stable when at an incline of 10 degrees. Recommended pole: Pryor Products, Inc. #135.

3. Ensure that the pole has locking wheels such that it can remain stationary on a 10 degree angle.
4. If the pole is on an incline, it may experience an initial settling movement prior to establishing a stable fix location, ensure that control of the pole is maintained until stable.
5. If the pole has the ability to extend, do not extend the height of the pole. Keep the pole at its lowest height setting.

Figure 4. The pole clamp



1. Pole clamp

Hospital Electronics System Password Access

By default, new Hospital Electronics Systems require you to enter a Merlin.net PCN username and password before you can use the system. This protects the privacy of patient information. If the system is in a secure area, and you are a Merlin.net PCN administrator, you can disable the Password Entry screen from the Settings screen.

If you are unable to gain access with the password, you can obtain a temporary password on the My Account page on the Merlin.net Patient Care Network Heart Failure Management Application. To access the system after you obtain a temporary password:

1. Enter your username and password on the User Log On screen.
2. Select the OK button.
   The system attempts to connect to the network.
3. Select the Cancel button.
   The system logs you in.

If you are unable to log in, contact Technical Support for additional assistance.

Patient and Hospital Electronics Systems

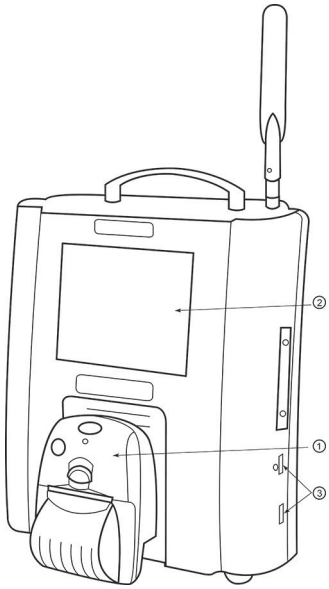
The CardioMEMS PA Sensor is implanted into a distal branch of the descending PA. Following implantation, patients are instructed to take pressure readings from home as directed by their physician. The information transmitted to the database is immediately available to clinicians for review. The information consists of pressure trend information and individual PA pressure waveforms.

The Patient and Hospital Electronics Systems have been designed to obtain information from the sensor. The functional components of the hardware include an electronics unit and an antenna. The antenna simultaneously sends a Radio Frequency (RF) signal to energize the sensor and measures the RF signal returned by the sensor. This returning signal is processed and stored in the electronics unit.

There are two types of electronics systems: the Patient Electronics System and the Hospital Electronics System. The Patient Electronics System is the primary means of monitoring. It is used at home by the patient to take regular measurements. The Hospital Electronics System is used during sensor implant and when the patient needs measurements taken in a clinical setting.

The Hospital Electronics System should be mounted on a portable pole stand with wheels and stored in the Catheterization Lab area or Heart Failure Clinic as needed by clinicians.

Figure 5. The Hospital Electronics System



1. Thermal printer
2. Touchscreen
3. USB ports

Antenna

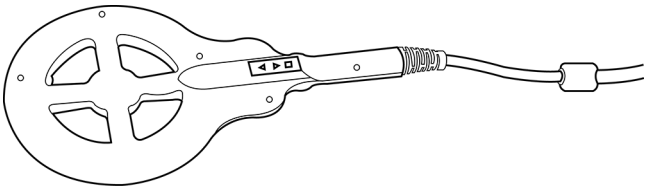
The antenna attached to the Hospital Electronics System is designed for ease of use during implant and for follow-up measurements in the hospital or clinic. The antenna is the means of coupling to the sensor and is connected to the electronics unit by a custom cable with a locking connector. During a measurement, the antenna is placed near the sensor. The antenna uses RF energy to power the sensor. When the sensor is energized, it returns an RF signal. The antenna receives the signal and sends it to the electronics system for processing into a pressure waveform.

The arrows on the antenna control the Search pressure, and the green square lets you take a reading.

Due to the design of the system, you can leave the antenna attached to the electronics unit at all times if desired.

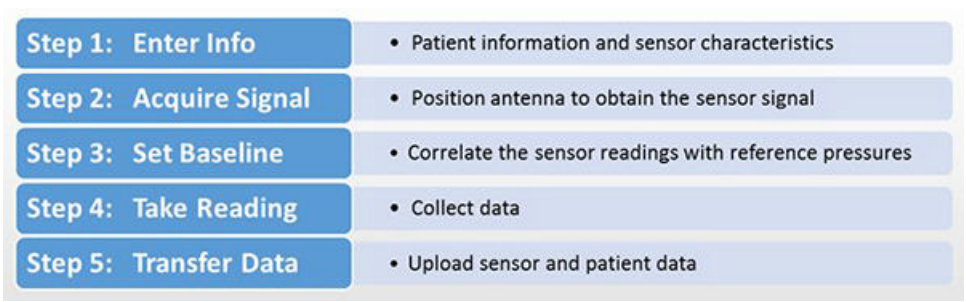
NOTE: The serial number on the antenna and on the electronics unit must match.

Figure 6. Antenna



Overview

Implant Procedure Overview



For detailed instructions, refer to the following sections:

- New Sensor Implant - Wireless Connection Available
- New Sensor Implant - No Wireless Connection Available

New Sensor Implant - Wireless Connection Available

This section presents using the Hospital Electronics System to perform a sensor implant when a wireless connection is available for communication with the Merlin.net Patient Care Network Heart Failure Management Application.

Before the Hospital Electronics can be used to measure a newly implanted sensor, the electronics must be set up with the following information:

- Patient Information

- Sensor Characteristics

Step 1: Enter Information

All Hospital Electronics Systems are equipped with cellular antennas. WiFi is an available accessory. The workflow presented in this section is recommended based on simplicity. These instructions expect that the conditions in your institution permit the use of wireless connectivity. If this is not possible in your institution see the section New Sensor Implant – No Wireless Connection Available below.

1. Patient Information: Prior to the first sensor implant of the day, use the Merlin.net Patient Care Network Heart Failure Management Application to enter the patient information for all of the patients expected to receive a CardioMEMS HF sensor in the cardiac catheterization lab that day. Please refer to the Merlin.net Patient Care Network Heart Failure Management Application Help Manual for details.

   Sensor Information: Each sensor has unique characteristics which must be loaded into the Hospital Electronics System. The sensor information is stored on a USB flash drive inside the sensor box. It is important that the sensor information loaded into the Hospital Electronics System matches the sensor implanted.

   Wait until the time of sensor delivery and then follow the instructions below on the Hospital Electronics System for each new sensor.
2. Insert USB flash drive from sensor package into the USB port.
3. Select New Implant button.
4. You will be presented with the list of patients that you entered into the Merlin.net Patient Care Network Heart Failure Management Application.
5. Select the desired patient from the list.
6. If prompted, insert the USB flash drive from the sensor package into the USB port. (System will only prompt if USB flash drive was not already inserted.)
7. After the sensor information is loaded, it will be displayed along with the patient information. Verify that Sensor Serial displayed matches the Serial Number printed on the sensor box.

The screens for these steps are shown in the following sequence.

Figure 7. Main screen, select New Implant.

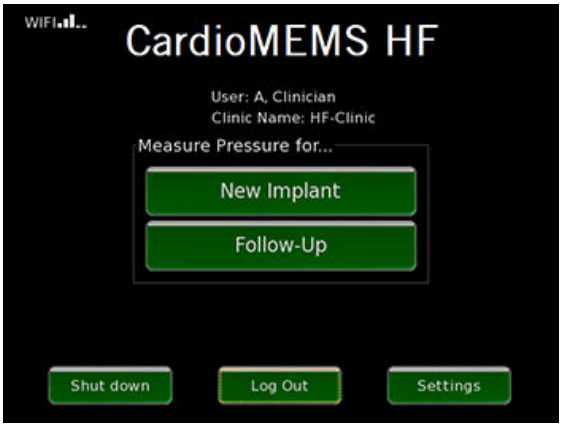


Figure 8. Select patient from list downloaded from Merlin.net Patient Care Network Heart Failure Management Application.

NOTE: All screenshots are simulations and do not represent actual patients or actual patient data.

Figure 9. Insert USB drive if prompted. This screen will not appear if USB drive was already inserted.

Figure 10. Verify patient and sensor information.

Step 2: Acquire Signal

Once you have loaded the patient and sensor information into the Hospital Electronics System and then implanted the sensor, the steps below describe how to set the pulmonary artery (PA) pressure baseline.

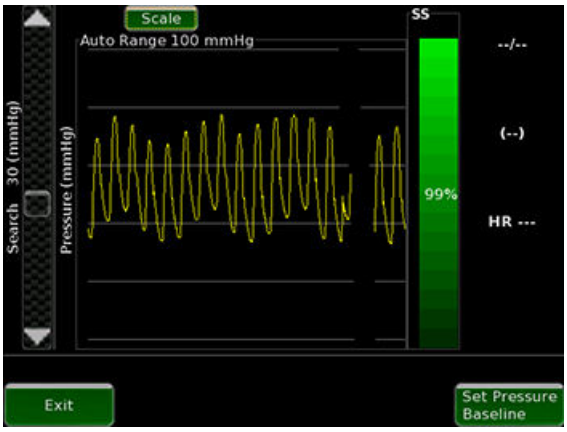
1. Place the antenna under the patient's back, approaching from the side where the sensor was placed. Antenna is not sterile. Sliding the antenna between the sheet and the table works well. Position the center of the antenna under the tip of the patient's shoulder blade on the side of the torso where the sensor is located.
2. The signal strength (SS) bar indicates the robustness with which the Hospital Electronics System is measuring the implanted sensor. If the signal strength bar is optimal (>70% and a green color, see figure below), go to the next step. If not, go to the section Optimize Signal Strength.

Step 3: Set Baseline

1. A pulmonary artery or Swan-Ganz [1] catheter is used to set the baseline pressure for the sensor. For an accurate sensor measurement, it is important to set up the pulmonary artery or Swan-Ganz catheter properly. See Pulmonary Artery Catheter Setup section.
2. Initially, you will observe that the pressure values on the right of the waveform are dashed out. This indicates that the PA pressure baseline has not been set.

[1] Swanz-Ganz is a registered trademark of Edwards Lifesciences Corporation.

Figure 11. Initial Pressure Waveform.

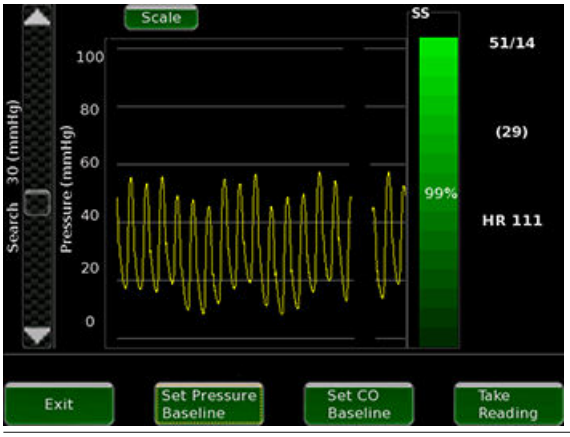


3. To Set the PA Pressure Baseline, wait for the screen to fill with a stable pressure waveform and then select the Set Pressure Baseline button.
4. Enter the mean pressure from the pulmonary artery catheter measurement and select the OK button.

Figure 12. Setting PA Pressure Baseline.

5. Wait for the screen to re-fill with a stable pressure waveform and then confirm that the sensor mean pressure matches the catheter PA mean pressure within +/- 1 mm Hg. Repeat the PA Baseline step as necessary to achieve a good match between measurements.

Figure 13. System after PA Pressure Baseline has been set.



6. Confirm that the height of the sensor pressure signal (i.e., pulse pressure (systolic – diastolic)) is within +/- 25% of the catheter pulse pressure. See Pulmonary Artery Catheter Setup section. Set the PA Pressure Baseline again, if necessary.
7. Setting the cardiac output baseline is an optional step.
8. To set the cardiac output (CO) baseline, you will need a reference value for cardiac output. This can be either thermodilution or modified Fick.
9. Select the button Set CO Baseline. The Hospital Electronics System will indicate that the baseline data is being collected and will prompt for the reference cardiac output once finished.

Figure 14. Enter Reference Cardiac Output to Set Baseline.

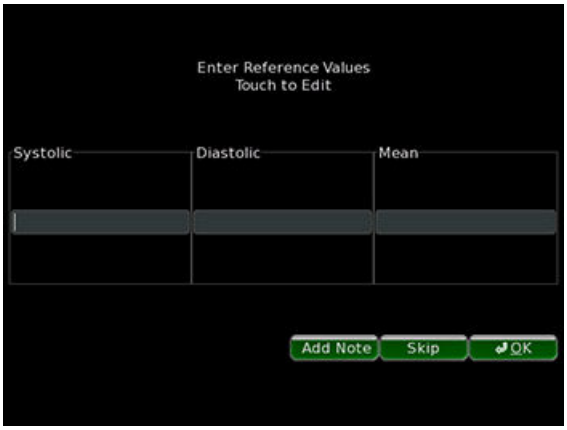
10. Enter the reference cardiac output value and select OK.

Step 4: Take Reading

Once you are satisfied with the PA pressure baseline, take as many pressure readings as desired. Establishing accurate baseline PA pressure at the time of implant is important to ensure accurate PA pressure readings from home.

1. Select the Take Reading button to capture pressure measurements.
2. The system will then prompt you to enter the comparative pulmonary artery catheter pressure values for reference. Enter the catheter values and select the OK button. The comparative pulmonary artery catheter pressure values are optional. They are used to visually check that the PA pressure values have the proper baseline and amplitude.

Figure 15. Enter Pulmonary Artery Catheter Pressure Values.



3. The captured reading is displayed graphically for confirmation. The colored horizontal lines indicate the catheter pressure values entered as reference. The green line indicates systolic pressure, blue indicates mean pressure, and red indicates diastolic pressure.

Figure 16. Pulmonary Artery Catheter Pressure Reading.

4. If the reading is acceptable, select the Yes button to save the reading. If the reading is unacceptable, select the No button and repeat the reading.

5. Re-confirm that the sensor mean pressure matches the catheter PA mean pressure within +/- 1 mm Hg. Check the setup and if necessary, set the PA Pressure Baseline again to achieve a good match between measurements.
6. Re-confirm that the height of the sensor pressure signal (i.e., pulse pressure (systolic – diastolic)) is within +/- 25% of the catheter pulse pressure. Check the setup and if necessary, set the PA Pressure Baseline again to achieve a good match between measurements.

Step 5: Transfer Data

Once the readings are complete, the Merlin.net Patient Care Network Heart Failure Management Application must be updated with the information. In the case a wireless data connection is available, this happens automatically. After the data is transferred, the system checks for software updates. Refer to the Software Update section for more information.

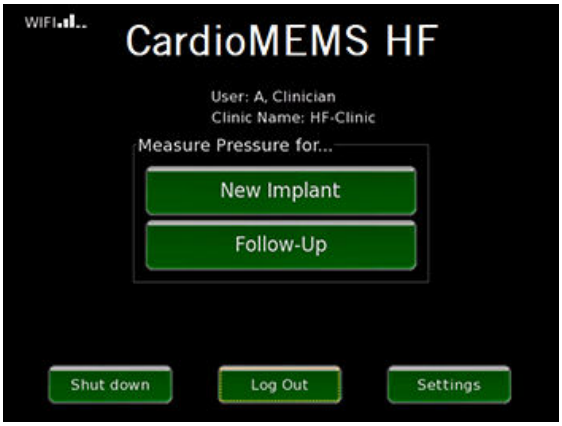
1. Select Exit from the data acquisition screen. If the user selects to print, the readings will print.
2. The baselines and readings will be automatically transmitted to the Merlin.net Patient Care Network Heart Failure Management Application.

Step 6: Shutting Down the System

To shut down the system:

1. Navigate to the Main screen.
2. Select Shut Down on the Main screen.

Figure 17. Main screen, Select Shut Down.



3. Allow the system to complete the shut-down sequence prior to disconnecting power from the system.
   CAUTION: Disconnecting power before the shut-down sequence is completed may cause file corruption.

New Sensor Implant – No Wireless Connection Available

This section presents the use of the Hospital Electronics System to perform a sensor implant when a wireless connection is not available for communication with the Merlin.net Patient Care Network Heart Failure Management Application. The patient information is entered manually on the Hospital Electronics System.

Before the Hospital Electronics can be used to measure a newly implanted sensor, the electronics must be set up with the following information:

- Patient Information
- Sensor Characteristics

Step 1: Enter Information

Each sensor has unique characteristics which must be loaded into the Hospital Electronics System. The sensor information is stored on a USB flash drive inside the sensor box. It is important that the sensor information loaded into the Hospital Electronics System matches the sensor implanted.

Wait until the time of sensor delivery and then follow the instructions below on the Hospital Electronics System for each new patient:

1. Insert USB flash drive from sensor package into the USB port.
2. Select New Implant.
3. Patient Information: Enter the patient information using the touch screen keyboard. To modify a field such as first name, simply touch it and the touch keyboard will appear. It is necessary to fill out the first and last name fields and the birthdate. The phone number field is optional. All of this information will appear on the website once implant is complete.
4. Sensor Information: Each sensor has unique characteristics which must be loaded into the Hospital Electronics System. The sensor information is stored on a USB flash drive inside the sensor box. It is important that the sensor information loaded into the Hospital Electronics System matches the sensor implanted.
5. If prompted, insert the USB flash drive from the sensor package into the USB port. (The system will only prompt if USB flash drive was not already inserted.)
6. After the sensor information is loaded, it will be displayed along with the patient information. Verify that Sensor Serial displayed matches the Serial Number printed on the sensor box.

The screens for these steps are shown in the following sequence.

Figure 18. Main screen, select New Implant.

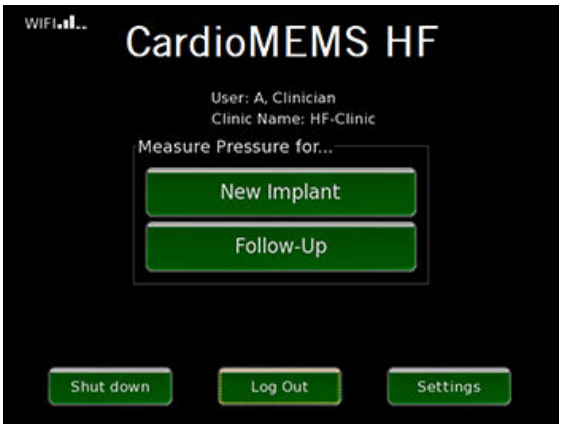


Figure 19. Enter patient demographic information.

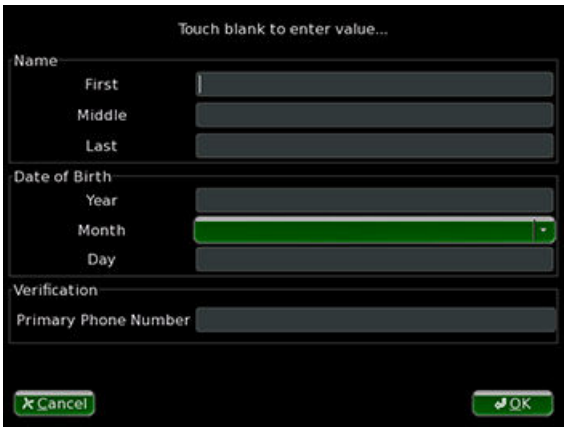


Figure 20. Enter patient information using touch keyboard.

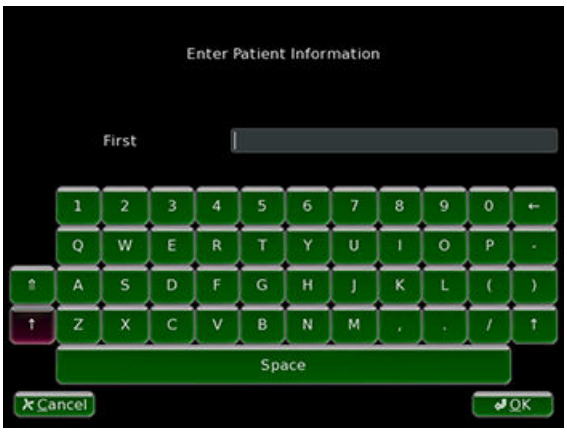


Figure 21. Insert USB drive if prompted. This screen will not be shown if the USB drive was already inserted.

Figure 22. Verify patient and sensor information.

Step 2: Acquire Signal

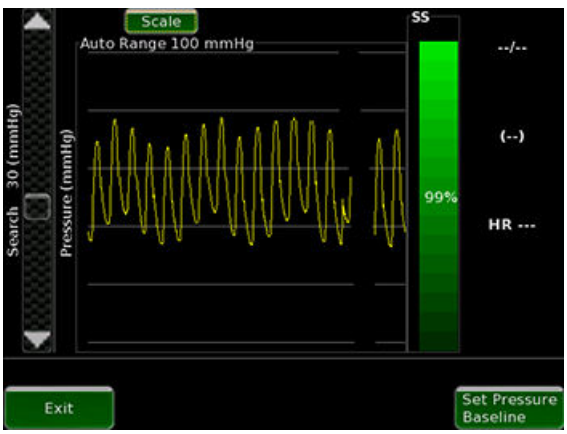
Once you have loaded the patient and sensor information into the Hospital Electronics System and then implanted the sensor, the steps below describe how to set the pulmonary artery (PA) pressure baseline.

1. Place the antenna under the patient's back, approaching from the side where the sensor was placed. Position the center of the antenna under the tip of the patient's shoulder blade on the side of the torso where the sensor is located.
2. The signal strength (SS) bar indicates the robustness with which the Hospital Electronics System is measuring the implanted sensor. If the signal strength bar is optimal (>70% and a green color), go to the next step. If not, go to the Optimize Signal Strength section.

Step 3: Set Baseline

1. A pulmonary artery catheter is used to set the baseline for the sensor. For an accurate sensor measurement, it is important to set up the catheter properly. See Pulmonary Artery Catheter Setup section.
2. Initially, you will observe that the pressure values on the right of the waveform are dashed out. This indicates that the PA pressure baseline has not been set.

Figure 23. Initial Pressure Waveform.

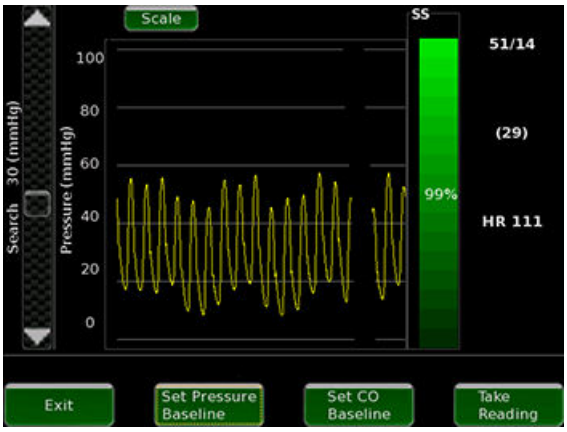


3. To Set the PA Pressure Baseline, wait for the screen to fill with a stable pressure waveform and then select the Set Pressure Baseline button.
4. Enter the mean pressure from the pulmonary artery catheter measurement and select the OK button.

Figure 24. Setting PA Pressure Baseline.

5. Wait for the screen to re-fill with a stable pressure waveform and then confirm that the sensor mean pressure matches the catheter PA mean pressure within +/- 1 mm Hg. Set the PA Pressure Baseline step again as necessary to achieve a good match between measurements.

Figure 25. System after PA Pressure Baseline has been set.



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7. Setting the cardiac output baseline is an optional step.
8. To set the cardiac output (CO) baseline, you will need a reference value for cardiac output. This can be either thermodilution or modified Fick.
9. Select the button Set CO Baseline. The Hospital Electronics System will indicate that the baseline data is being collected and will prompt for the reference cardiac output once finished.

Figure 26. Enter Reference Cardiac Output to Set Baseline.

10. Enter the reference cardiac output value and select OK.

Step 4: Take Reading

Once you are satisfied with the PA pressure baseline, take as many pressure measurements as desired. Establishing accurate baseline PA pressure at the time of implant is important to ensure accurate PA pressure readings from home.

1. Select the Take Reading button to capture pressure measurements.
2. The system will then prompt you to enter the comparative catheter pressure values for reference. Enter the catheter values and select the OK button. The comparative pulmonary artery catheter pressure values are optional. They are used to visually check that the PA pressure values have the proper baseline and amplitude.

Figure 27. Enter Pulmonary Artery Catheter Pressure Values.

3. The captured reading is displayed graphically for confirmation. The colored horizontal lines indicate the entered catheter pressure values entered as reference. The green line indicates systolic pressure, blue indicates mean pressure, and red indicates diastolic pressure.

Figure 28. Pulmonary Artery Catheter Pressure Reading.

4. If the reading is acceptable, select the Yes button to save the reading. If the reading is unacceptable, select the No button and repeat the reading.
5. As was discussed in the Step 2: Acquire Signal section above, re-confirm that the sensor mean pressure matches the catheter PA mean pressure within +/- 1 mm Hg. Check the setup and if necessary, set the PA Pressure Baseline again to achieve a good match between measurements.
6. As was also discussed in the Step 2: Acquire Signal section above, re-confirm that the height of the sensor pressure signal (i.e., pulse pressure (systolic – diastolic)) is within +/- 25% of the catheter pulse pressure. Check the setup and if necessary, set the PA Pressure Baseline again to achieve a good match between measurements.

Step 5: Transfer Data

Once the readings are complete, the Merlin.net Patient Care Network Heart Failure Management Application must be updated with the information. A USB flash drive is used to accomplish this.

1. Select Exit from the data acquisition screen. If the user selects to print, the readings will print.
2. You will be prompted to save the information to a USB flash drive.

   NOTE: A USB flash drive is provided in the sensor box with each sensor, but you can use any USB flash drive. Most commercial USB flash drives will be compatible with both the electronics system and the computer used to access the Merlin.net Patient Care Network Heart Failure Management Application.

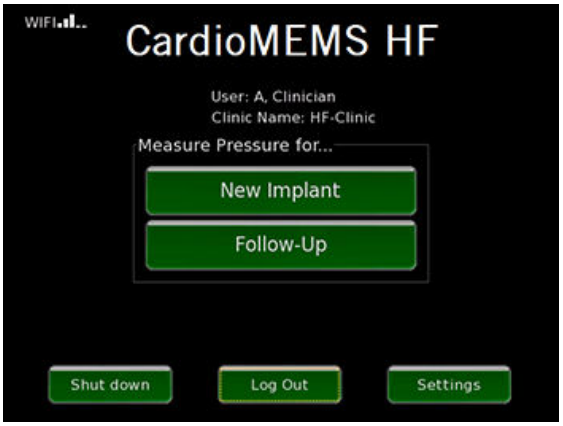
Figure 29. Save Implant Data to the USB Flash Drive.

Step 6: Shutting Down the System

To shut down the system:

1. Navigate to the Main screen.
2. Select Shut Down on the Main screen.

Figure 30. Main screen, Select Shut Down.



3. Allow the system to complete the shut-down sequence prior to disconnecting power from the system.
   CAUTION: Disconnecting power before the shut-down sequence is completed may cause file corruption.

Merlin.net Patient Care Network Heart Failure Management Application Setup

The Merlin.net Patient Care Network Heart Failure Management Application is the central window from which to view the status of your patient. After the implant you need to confirm the proper setup of your patient on the website.

The following important information is updated on the website after implant:

- The link between your medical institution and the patient. Patient data is only visible to users associated with your medical institution.
- The baselines and readings from the implant procedure. This allows accurate trending once your patient begins to take readings at home.

Refer to the Merlin.net Patient Care Network Heart Failure Management Application Help Manual for specific website setup instructions.

You will not be able to set up the Patient Electronics until the website has been set up with your patient's information.

Patient Electronics System Setup

After the website has been properly set up, the Patient Electronics must be set up before your patient can begin taking readings at home.

Figure 31. Patient Electronics System

The Patient Electronics will be set up with the following:

- Patient Information
- Sensor Characteristics
- Baseline Information

There are two primary ways to set up the electronics with this information.

1. From the website using wireless connectivity
2. Locally on the electronics using the USB flash drive

A third option is available as a backup method in case the primary methods are unavailable See Manual Setup Instructions section. In this option, no USB flash drive is used and all of the information is entered via the touch screen.

Setup – Wireless Connection Available

Most Patient Electronics Systems will have cellular connections. Follow these steps if a cellular connection is available.

1. When the system starts, it will prompt for the language and country. To select the language and country, press the Next button until the desired language or country appears and then press the Select button.
2. To enter the sensor serial number, select the Enter button and then type in the serial number using the keyboard.
3. The Patient Electronics System will then download the necessary information for the patient from the Merlin.net Patient Care Network Heart Failure Management Application and then prompt you to confirm the information.
4. When the system is successfully setup the system will display the patient's name above the Start button.
5. To shut down the system, press the Options button on the Start screen and then press the Shut Down button. Allow the system to complete the shut-down sequence prior to removing power from the system. Failure to do so may cause file corruption.

The following screens illustrate the sequence.

Figure 32. Enter the language.

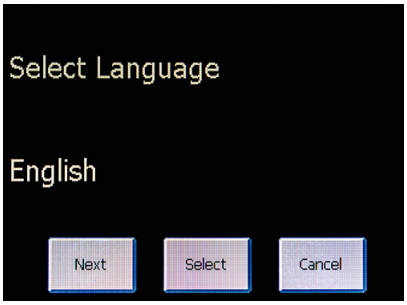


Figure 33. Enter the country.

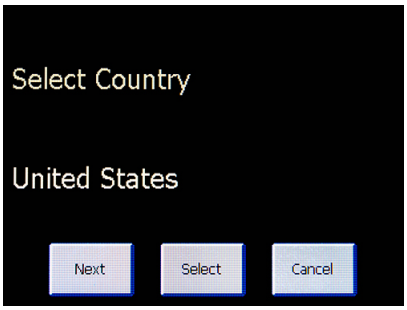


Figure 34. System prompts to enter sensor serial number.

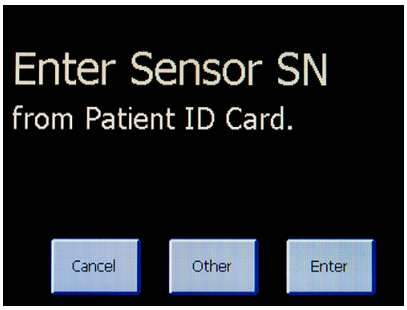


Figure 35. Confirm patient and sensor information.

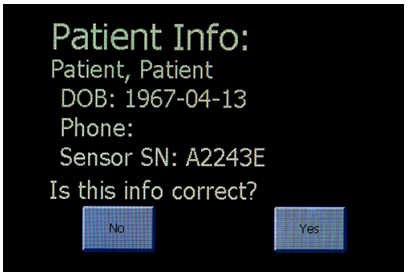


Figure 36. Patient name will be displayed on starting screen.

Setup - No Wireless Connection Available

When the system starts, wireless connectivity may be unavailable for the following reasons.

- The system has a dial up telephone modem.
- If the system has a cellular modem, but the cellular signal is weak, move the system to try to get a better signal. If successful, follow the wireless connection setup steps above. If not, follow the instructions below.

1. Insert a USB flash drive into the USB port of the computer.
2. On the Merlin.net Patient Care Network Heart Failure Management, use the Export feature beneath the More Actions link on the Patient Profile tab for your patient. For more information consult the Merlin.net Patient Care Network Heart Failure Management Application Help Manual.
3. On the Patient Electronics System, select the Other button.
4. Select the OK button on the Insert Website USB screen.
5. If there are multiple patient files found on the USB flash drive, you will be shown screens for each patient file on the USB flash drive. Select the Nxt Pat button to move to the next patient. Select the Load button to load the correct patient.
6. When prompted to confirm the information, review the information. Ensure the name and sensor serial number are correct.
7. When the system is successfully setup the electronics unit will display the patient's name above the Start button.
8. To shut down the system, press the Options button on the Start screen and then press the Shut Down button. Allow the system to complete the shut-down sequence prior to removing power from the system. Failure to do so may cause file corruption.

Figure 37. Select the Other button.

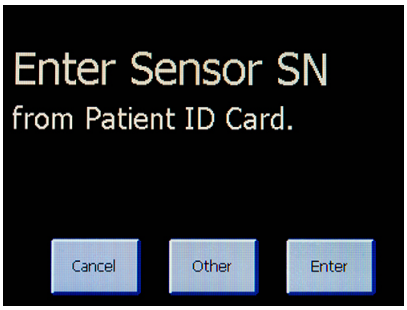


Figure 38. USB screen.

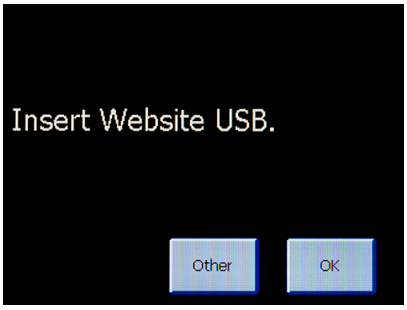


Figure 39. Confirm patient and sensor information.

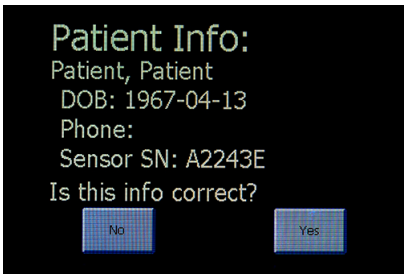
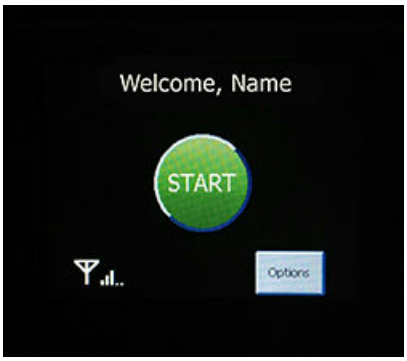


Figure 40. Patient name will be displayed on start screen.



Patient Training

Discuss the information in the Patient Instructions and Patient System Guide with your patient before and after sensor implantation. For additional copies of the patient's guide, contact Technical Support. You should also explain the established benefits and risks of the CardioMEMS HF System with the patient. Discuss the home measurement schedule and the intended use of the system to assist their healthcare provider in the management of their heart failure. Refer to the Patient System Guide for details.

Train the patient how to set up and use their Patient Electronics System prior to their discharge from the hospital. Make sure that the patient is able to operate all of the connectors. For the best results have the patient or family member run through all the steps from start to finish.

1. Have the patient lie supine on the pillow.

   The patient should position their torso with the center of the pillow directly under the sensor. Typically this means that the tip of the shoulder blade nearest the sensor will be centered on the pillow. Use the same antenna position that gave the optimal signal during the implant procedure. The typical location for the sensor is on the left side. Check the patient's records to confirm actual location.

2. After the patient is in position, have the patient press either the Start button on the touchscreen or the round green button below the touchscreen.

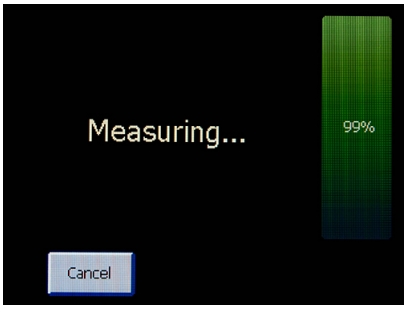
   The system will guide the patient with voice prompts. The screen below appears while the system searches for a signal.

Figure 41. System prompts to change position.

If the shift position screen appears, have the patient shift their position to find the best position. Once a good signal is available, the system will indicate with the voice prompt “Good Position on Pillow, Stay Still” and then begin to play music.

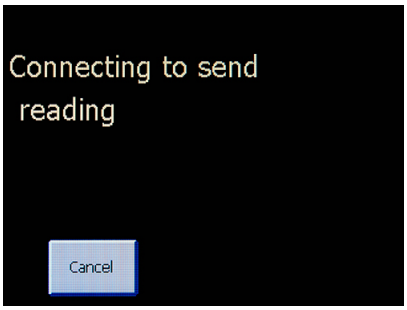
WARNING: Avoid placing the handheld unit directly on the pillow during a reading.

Figure 42. Reading in Progress.



A reading takes approximately 18 seconds to complete. This allows the system to average multiple heart beats over several breaths. When the reading is complete, the system will attempt to send the reading.

Figure 43. Connection in Progress.



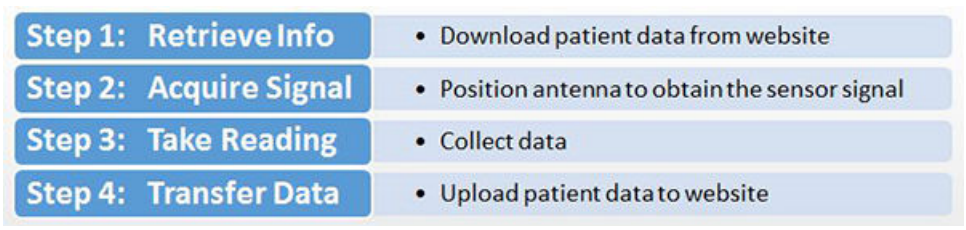
If cellular coverage is available, the system will send the data and shut down following transmission.

If wireless coverage is not available or if the system uses a dial-up connection, select Cancel to stop the system from continuing to attempt the connection. Explain to the patient that their system will automatically send the data from their home and automatically shut down afterwards. If the system is unable to transfer the readings to the website they will be stored for later transmission.

3. Once the system successfully sends the reading, it will automatically shut down. During training, if you do not wish the system to shut down, select ‘Cancel’ while it is sending. Allow the system to complete the shut-down sequence prior to disconnecting power from the system. Failure to do so may cause file corruption. If the automatic shut- down was cancelled, shut the system down by pressing the Options button on the Start screen, followed by Shut Down.
4. If the system has shut down, restart the system to take additional training readings.

Overview

Figure 44. Follow-up Reading Overview



For detailed instructions, refer to the following sections:

- Follow-Up Reading - Wireless Connection Available
- Follow-Up Reading - No Wireless Connection Available

Follow-Up Reading – Wireless Connection Available

When your patient returns to your institution for follow up visits, you will use the Hospital Electronics System to take follow-up pressure readings. If your Hospital Electronics System has wireless connectivity through WiFi or a cellular connection, all of the patients on the Merlin.net Patient Care Network Heart Failure Management Application will be available on the system.

Step 1: Retrieve Information

1. Select Follow-Up.
2. You will be presented with the list of patients that are available on this electronics unit.
3. Select the Check HF Website button to refresh the list from the Merlin.net Patient Care Network Heart Failure Management Application.
4. The list can be searched by entering information into the search box at the top.
5. Select the desired patient from the list.
6. Select OK.

Review the following sequence screens to perform these actions.

Figure 45. Select Follow-Up.

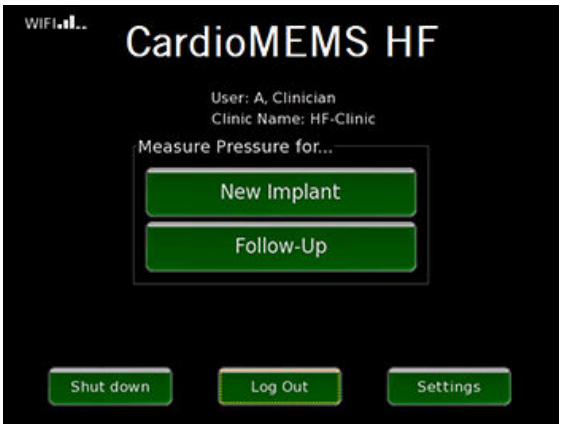


Figure 46. Select desired patient from the list.

Step 2: Acquire Signal

1. Place the antenna under the patient's back, approaching from the side where the sensor was placed. Position the center of the antenna under the tip of the patient's shoulder blade on the side of the torso where the sensor is located. The preferred location for sensor placement is on the left side. Check your patient's chart to confirm.
2. The system will prompt if pulmonary artery catheter pressure readings are available. Select Yes or No. This allows the system to capture these values for reference if they are available.
3. The signal strength (SS) bar indicates the robustness with which the Hospital Electronics System is measuring the implanted sensor. If the signal strength bar is optimal (>70% and a green color), go to the next step. If not, go to the section Optimize Signal Strength.

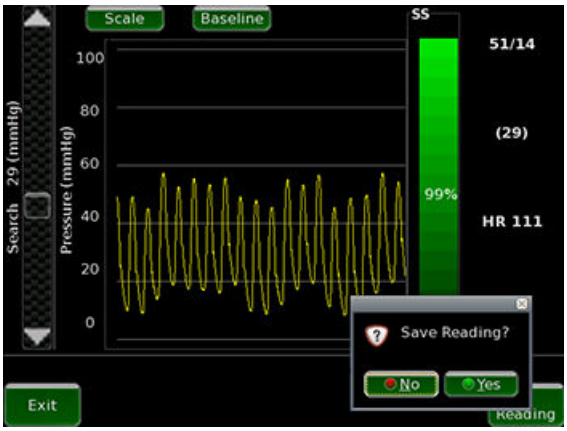
Step 3: Take Reading

The system will allow you to take as many readings as needed.

1. Select the Take Reading button to capture pressure measurements.

2. If available, the system will then prompt you to enter the comparative catheter pressure values for reference. Enter the values and select the OK button.

Figure 47. Follow-up Pressure Reading.



The captured reading is displayed for confirmation. The colored horizontal lines indicate the catheter pressure values entered as reference (if available). The green line indicates systolic pressure, blue indicates mean pressure, and red indicates diastolic pressure.

3. If the reading is acceptable, select the Yes button to save the reading. If the reading is unacceptable, select the No button and repeat the reading.

Step 4: Transfer Data

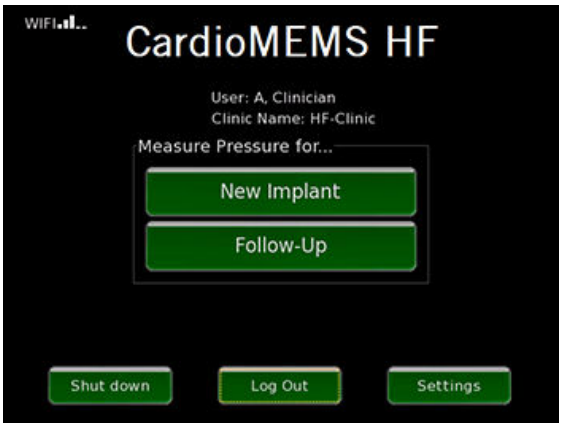
1. Select Exit from the data acquisition screen. If the user selects to print, the readings will print.
2. Since your system has a wireless connection, the baselines and readings will be transmitted to the Merlin.net Patient Care Network Heart Failure Management Application.

Step 5: Shutting Down the System

To shut down the system:

1. Navigate to the Main screen.
2. Select Shut Down on the Main screen.

Figure 48. Main screen, Select Shut Down.



3. Allow the system to complete the shut-down sequence prior to disconnecting power from the system.

CAUTION: Disconnecting power before the shut-down sequence is completed may cause file corruption.

Follow-Up Reading – No Wireless Connection Available

When your patient returns to your institution for follow up visits, you may use the Hospital Electronics System to take follow-up pressure readings. On the first follow-up visit, you will need to retrieve the information on your patient from the Merlin.net Patient Care Network Heart Failure Management Application. You will also need to retrieve the updated information on your patient if there have been any repeat right heart catheterizations where the baseline changed.

Step 1: Retrieve Patient Information

1. Insert a USB flash drive into the USB port of the computer.

2. On the Merlin.net Patient Care Network Heart Failure Management Application, use the Export feature beneath the More Actions link on the Patient Profile tab for your patient. For more information consult the Merlin.net Patient Care Network Heart Failure Management Application Help Manual.

   NOTE: You can use any USB drive. Most commercial USB drives will be compatible with both the Hospital Electronics System and the computer used to access the Merlin.net Patient Care Network Heart Failure Management Application.
3. On the Hospital Electronics System, select Follow-Up.
4. You will be presented with the list of patients that are available on this electronics unit. Select the button 'Add…' below the list.
5. Insert the USB Drive when prompted.
6. Review and confirm the patient and sensor information.
7. Select OK.

The screens for this sequence are presented below.

Figure 49. Select Follow-Up.

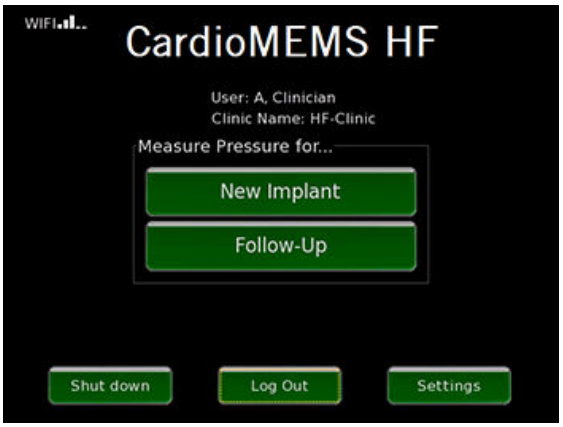


Figure 50. In this case, the patient is not available, select 'Add…' from below the list.

Figure 51. Insert USB Drive when prompted.

Figure 52. Confirm patient and sensor information.

Step 2: Acquire Signal

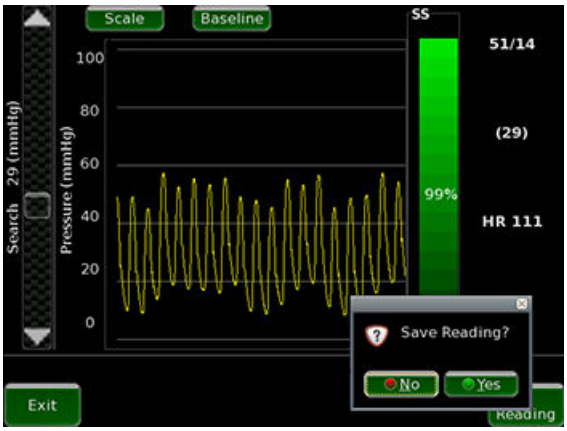
1. Insert the antenna under the patient's back, approaching from the side where the sensor was placed. Position the center of the antenna under the tip of the patient's shoulder blade on the side of the torso where the sensor is located. The preferred location for sensor placement is on the left side. Check your patient's chart to confirm.
2. The system will prompt if pulmonary artery catheter pressure readings are available. Select Yes or No. This allows the system to capture these values for reference if they are available.
3. The signal strength (SS) bar indicates the robustness with which the Hospital Electronics System is measuring the implanted sensor. If the signal strength bar is optimal (>70% and a green color), go to the next step. If not, go to the section Optimize Signal Strength.

Step 3: Take Reading

The system will allow you to take as many readings as needed.

1. Select the Take Reading button to capture pressure measurements.
2. If available, the system will then prompt you to enter the comparative catheter pressure values for reference. Enter the values and select the OK button.

Figure 53. Follow-up Pressure Reading.



The captured reading is displayed for confirmation. The colored horizontal lines indicate the catheter pressure values entered as reference (if available). The green line indicates systolic pressure, blue indicates mean pressure, and red indicates diastolic pressure.

3. If the reading is acceptable, select the Yes button to save the reading. If the reading is unacceptable, select the No button and repeat the reading.

Step 4: Transfer Data

For routine follow-ups, transferring the patient information and readings back to the Merlin.net Patient Care Network Heart Failure Management Application is an optional step. The advantage is that all follow-up readings will be visible on the website along with the home readings.

If there is any change to the baseline it is important to transfer the information back to the Merlin.net Patient Care Network Heart Failure Management Application so that the system in your patient's home uses the updated baseline.

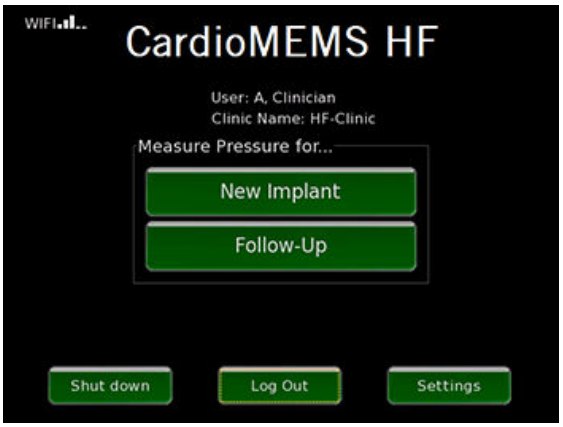
1. Select Exit from the data acquisition screen. The readings will print.
2. You will be prompted to save the information to a USB flash drive.
3. Insert the USB flash drive and select OK.
4. Import the information into the Merlin.net Patient Care Network Heart Failure Management Application.

Step 5: Shutting Down the System

To shut down the system:

1. Navigate to the Main screen.
2. Select Shut Down on the Main screen.

Figure 54. Main screen, Select Shut Down.



3. Allow the system to complete the shut-down sequence prior to disconnecting power from the system.
   CAUTION: Disconnecting power before the shut-down sequence is completed may cause file corruption.

Locating Sensor Signal

This section outlines procedures to help locate the sensor signal.

A. Optimize Signal Strength

Follow this procedure if the signal strength is not optimal (<70% or not green). Use fluoroscopy to improve the position of the antenna relative to the implanted sensor.

1. Align the center of the antenna with the sensor and adjust the antenna to maximize the signal strength.
   If the signal strength is optimal (>70%), return to the section Acquire Sensor Signal and resume where you left off. If not, go to step 2 below.
   NOTE: The system reads the PA pressure by sending out RF signals to the sensor and then detecting a return signal from the sensor. These RF signals can reflect from the building structure and can cause the system to detect a strong signal level that is not the true sensor signal. These technically suspect readings do not have a pulse like the pulmonary artery pressure. The software aids the user in identifying whether or not a signal is pulsatile. If the system detects that the signal is pulsatile, the Signal Strength bar will turn green. If the system determines that the signal is not pulsatile, the Signal Strength bar will turn blue. It is possible that the system could identify an actual signal with extremely low pulse amplitude as non-pulsatile, so user-discretion is advised when using the colored pulsatility indication.

Figure 55. Pulsatile signal strength.

Figure 56. Non-pulsatile signal strength.

2. Adjust the pressure search scrollbar on the left side of the acquisition screen signal tuner up or down in small increments. Try to match the Search pressure value displayed next to the scrollbar to the mean pulmonary artery catheter pressure value.

   If the signal strength is optimal (>70%), return to the section Acquire Sensor Signal and resume where you left off. If the signal is not acquired after changes in the scrollbar position, return the slider bar to the original starting position and go to step 3 below.
3. Shift the antenna position.

   If the signal strength is optimal (>70%), return to the section Acquire Sensor Signal and resume where you left off. If not, go to step 4 below.
4. If the sensor orientation is fully lateral, lift the outer edge of the antenna into a partially tilted or lateral orientation from the side of the rib cage to detect the sensor.

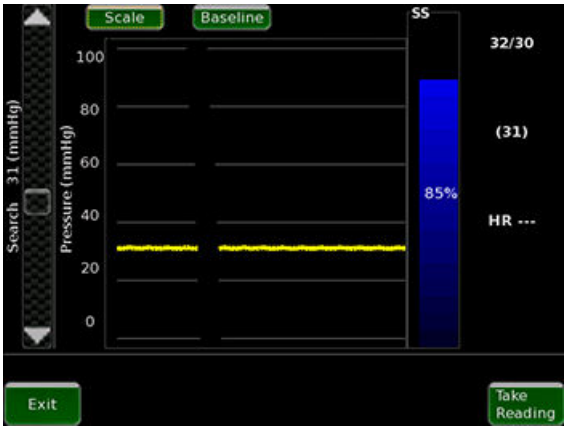
B. Technically Suspect Readings

Technically suspect readings are readings which result from a signal other than the sensor.

If you receive technically suspect readings that have a high signal strength (> 70%) within the search range of the sensor:

- Be aware of the angulation of the sensor relative to the antenna and have the patient shift positions until the suspect reading minimizes.
- Place the antenna between the operator and the patient.
- Relocate to a different room.
- See section Solutions for Interference below.

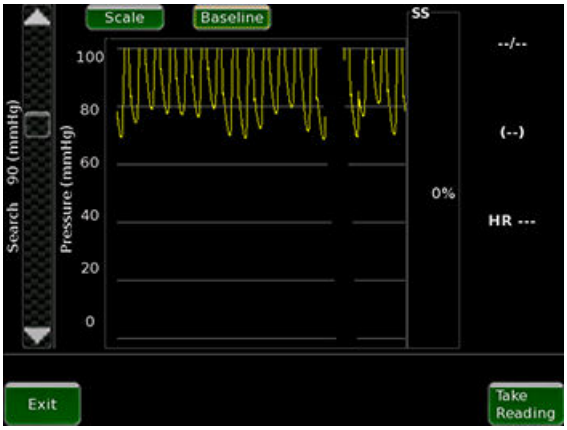
Figure 57. Technically suspect reading with high signal strength. Pressure waveform is non-pulsatile with no inflection for the heart beat. Signal strength bar is blue.



If the signal strength indicator is 0, the system is most likely measuring a technically suspect reading and the system is purposely forcing the signal strength to 0. To resolve this:

- Use the search scrollbar to move off this reading by repeatedly (and quickly) pressing the search scrollbar button several times.
- Move the search scrollbar in the direction that makes most sense according to physiological pressures.
- See section Solutions for Interference below.

Figure 58. Technically suspect reading with low signal strength. Signal is pulsatile with a heart beat but is at a high pressure that does not make sense for this patient.



For either high or low signal strength technically suspect readings, if the reported mean pressure reads above or below the expected value from the pulmonary artery catheter:

- Increase the mean of the search scrollbar if it's too low.
- Decrease the mean of the search scrollbar if it's too high.

C. Distance

You can improve the signal if the sensor and antenna are located close together. To decrease the distance between the sensor and the antenna:

- Ask the patient to orient and locate the antenna over the position of the sensor.
- Ask the patient to press the antenna firmly into their back as much as is still comfortable.
- Ask the patient to remove all metallic objects.
- Have the patient shift into different positions.

D. Angulation

The signal strength is strongest when the antenna and sensor are parallel. Try these steps to change the angulation:

- Ask the patient to orient and locate the antenna over the position of the sensor.
- Adjust the search scrollbar until the mean pressure reads near the expected value.
- Ask the patient to press the antenna firmly into their back as much as is still comfortable.

E. Solutions for Interference

To reduce interference:

- Reduce the amount of metal in the vicinity of the sensor
- Reduce the number of electrical equipment and cables in the area
- Avoid the use of power strips and poorly grounded outlets when possible
- Move the C-arm away from the interrogation site
- Uncross guidewire
- Move or angle the antenna away from implantable devices
- Route ECG leads away from the area which the antenna will be located during a reading

Troubleshooting the Patient Electronics System

Table 1. Troubleshooting

Problem	Symptom	Solution
Cannot get a signal	Green bar never goes high Voice continues to indicate low signal Not able to complete a reading successfully	Check for any noticeable damage to the unit. Make sure there is no metal near the pillow. Make sure there is no electric blanket near the pillow. Reposition yourself on the pillow. Contact your clinic.
Reading completes but cannot send data to your doctor	Error message says to check connections Error message says reading cannot be sent	Check the USB cellular adapter, phone line or Wi-Fi adapter. Make sure the phone line is working or you are getting adequate signal strength on your wireless connection. Make sure the phone line is not busy. Make sure your Wi-Fi network name and password are correct. Make sure the electronics unit is calling the correct number.

Table 1. Troubleshooting

Problem	Symptom	Solution
		Contact your clinic.
Touchscreen does not respond	Buttons are not activated by repeated presses	Turn off the system by holding in the power button on the back of the electronics unit for greater than 5 seconds. Turn on the system and retry to use the touchscreen. If the problem is not resolved, contact your clinic.
Takes a long time to get a reading	Takes a long time (>30 seconds) to get a good signal Unit loses signal during reading and must re-start	Reposition yourself on the pillow until the green bar shows a higher signal strength. Make sure there are no electronics or metal in the vicinity of the measurement that may cause interference. Use the orientation ball to find the correct position. Contact your clinic.
Reading completes but is rejected by system	Error message says to repeat reading and reposition pillow away from any cords or metal objects	Remove any cords or metallic objects near the pillow or the pillow cable. Make sure there is no metal near the pillow. Make sure there is no electric blanket near the pillow. If you have a waterbed, take the measurements in another room. Contact your clinic.
Numeric error message	Error message with a number appears on the screen	Note the error. Click the OK button to acknowledge the error, wait for the error to transmit, and let the electronics unit shut down. Contact your clinic. You will not be able to take your reading.
	Error #0	There is a problem with the connections in the system such that important information cannot be sent.
	Error #1	The electronics system recorded an obviously incorrect value for the atmospheric pressure.
	Error #2	The two atmospheric pressure sensors in the electronics system do not agree.
	Error #3	Important data needed to make a measurement was not available.
	Error #4	The internal settings values needed to make a measurement were missing or damaged.
	Error #5	The atmospheric pressure sensor indicated an error in recording pressure or temperature.
	Error #6	An important part of the software was not able to run.
Numeric warning message	Warning message with a number appears on the screen	Note the warning. Retry the steps that caused the warning. If the warning appears a second time, contact your clinic. Continue to take your readings if possible.
Time of Day Clock is incorrect	Warning #5 message appears on the screen	Note the warning. Turn off the electronics unit from the Options menu. Restart the electronics unit. If the warning appears a second time,the time back-up battery may be dead. Continue to take readings until you are able to replace the battery. To replace the battery: 1. Use a screwdriver to remove the access door marked with a battery symbol on the back panel of the electronics. 2. Turn off and unplug the unit. 3. Remove the screws on the access door. Once the door is removed, note the “+” and “-“ symbols which show the direction of the battery. 4. Replace the battery (type BR2032) and reinstall the access door. Contact your clinic if this does not resolve the issue.

Pulmonary Artery Catheter Setup

1. The pulmonary artery catheter is used to set the baseline for the sensor. For an accurate sensor measurement, it is important to set up the catheter properly. Ensure the transducer has been properly leveled and zeroed to atmospheric pressure. If there are any concerns, repeat the setup.
2. It is important to confirm that the pulmonary artery catheter PA pressure waveform appears to be valid with minimal waveform distortion due to measurement artifact.

   Potential forms of measurement artifact include catheter whip, air bubbles in the pressure line, or catheter tip wedging. If artifact is present, address the potential sources of this artifact per the standard procedures for fluid-filled catheter monitoring until the PA pressure waveform appears to be reliable with minimal waveform artifact.

   Confirm that the pulmonary artery catheter produces a steady mean pressure value.

3. Once the system is measuring the pressure, confirm that the height of the sensor pressure signal (i.e., pulse pressure (systolic – diastolic)) is within +/- 25% of the catheter pulse pressure.

   If not, confirm that any monitoring artifact has been sufficiently minimized. If changes are made to minimize pulse pressure measurement artifact result in a discrepancy between mean pressures, set the PA Pressure Baseline again after such changes are made. If the PA pressure waveform has artifact minimized and pulse pressures are not within +/- 25%, repeat the sensor signal acquisition steps until pulse pressures match within +/-25%.

Manual Setup Instructions

The instructions above for New Sensor Implant, Patient Electronics System Setup and Follow-up Readings will cover situations where wireless communication is available and/ or when USB flash drive transfer is available. As a backup, all information can be entered manually into the system.

New Sensor Implant

Each sensor has unique characteristics which must be loaded into the Hospital Electronics System. The sensor information for these steps is printed on the sensor box.

Wait until the time of sensor implant and then follow these instructions for each new sensor:

1. Select New Implant.
2. Enter the patient information using the touch screen keyboard. To modify a field such as first name, simply touch it and the keyboard will appear. It is necessary to fill out the first and last name fields and the birthdate. The phone number is optional. All of this information will appear on the website once implant is complete.
3. When prompted for the USB flash drive from the sensor package, select 'Enter Manually'.
4. Use the touch screen to enter the sensor serial number and calibration code using the label on the sensor package.
5. After the sensor information is loaded, it will be displayed along with the patient information. Verify that Sensor Serial displayed matches the Serial Number printed on the sensor box.

The screens for these steps are shown in the following sequence.

Figure 59. Starting screen, select New Implant.

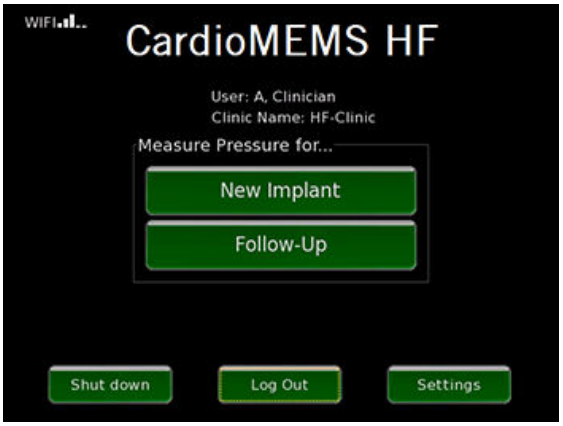


Figure 60. Enter patient demographic information.

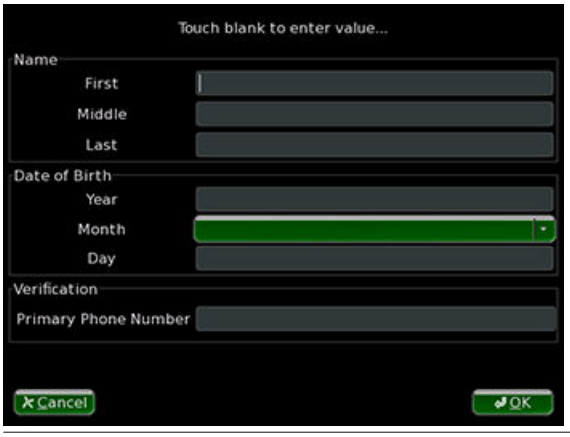


Figure 61. Enter patient information using touch keyboard.

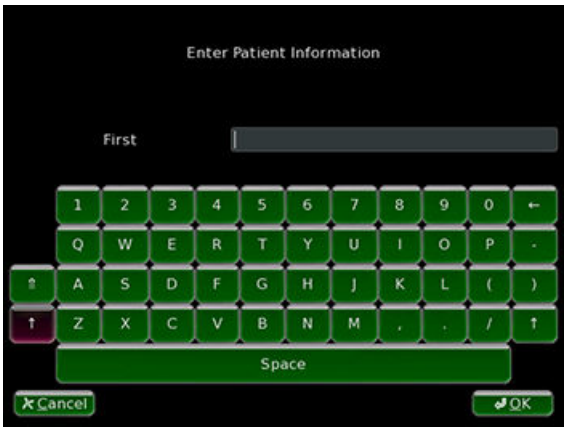


Figure 62. For manual entry of sensor information, touch ‘Enter Manually’.

Figure 63. Enter sensor information from sensor package.

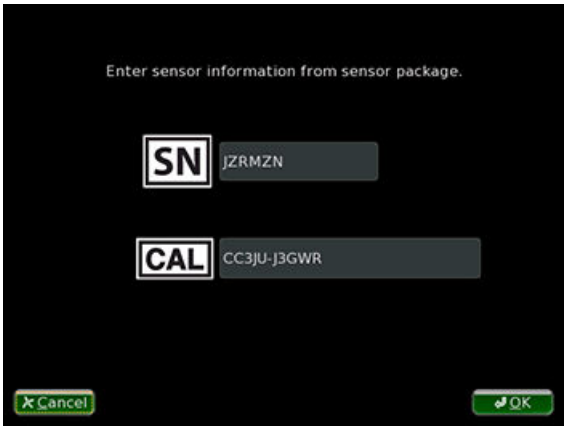


Figure 64. Verify patient and sensor information.

Patient Electronics System Setup

This is a backup option if the cellular connection is unavailable and you are unable to use a USB flash drive to retrieve the sensor information from the Merlin.net Patient Care Network Heart Failure Management Application.

1. These steps will require the patient information, the sensor characteristics and the baseline information be available. In addition, a 4 digit code is needed from the website. All of this information is available on the implant report which is printed from the Merlin.net Patient Care Network Heart Failure Management Application.
2. The Patient Electronics System powers up to an Enter Sensor SN screen. On this screen, select the Other button until you see the Enter Manually screen.
3. Select the OK button.
4. Enter the desired fields using the touch screen keyboard.
5. When prompted to confirm the information, review the information. Ensure the name and sensor serial number are correct.
6. If the information is incorrect, select the No button to repeat the process. You may need to return to the Merlin.net Patient Care Network Heart Failure Management Application to confirm that the information is correct.
7. When the system is successfully setup the electronics unit will display the patient's name above the Start button.

Figure 65. Select the Other button.

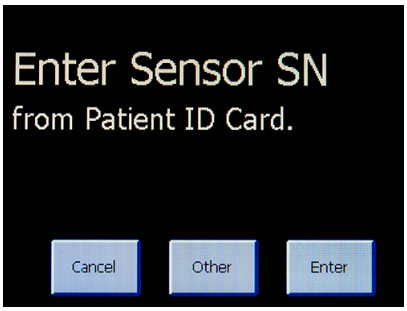


Figure 66. Enter Manually screen.

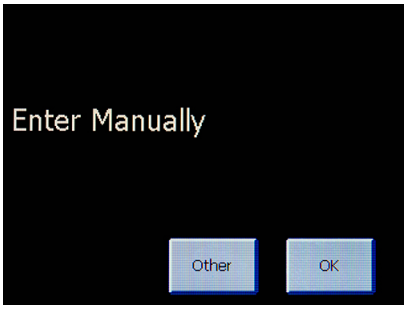


Figure 67. Enter the information from the implant report printed from the website.

Figure 68. Confirm patient and sensor information.

Figure 69. Patient name will be displayed on starting screen every time the system is started.

Follow-Up

1. Select Follow-Up.
2. You will be presented with the list of patients that are available on this electronics unit. Select the button ‘Add…’ below the list.
3. Select ‘Enter Manually’.
4. Enter the information from the Implant Report using the touch screen keyboard.
5. Review and confirm the patient and sensor information.
6. Select OK.

For this sequence, review the screens below.

Figure 70. Select Follow-Up.

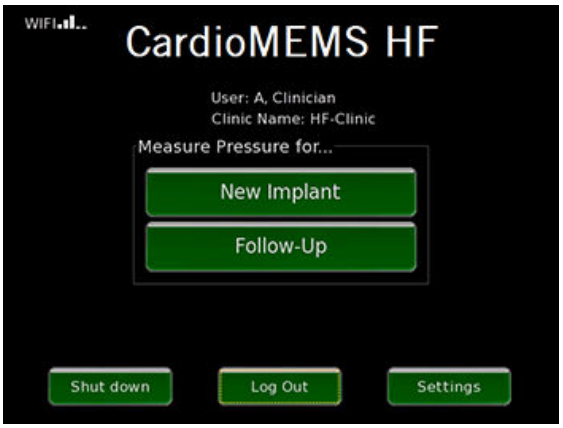


Figure 71. In this case, the patient is not available, select 'Add…' from below the list.

Figure 72. Select Manual Entry when prompted.

Figure 73. Enter the patient and sensor information.

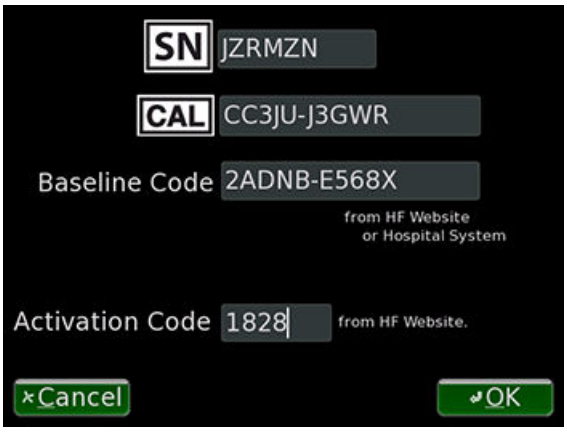


Figure 74. Confirm patient and sensor information.

Additional Hospital Electronics System Functions

A. Wireless Connectivity Setup

The Hospital Electronics System can be configured to communicate with the Merlin.net Patient Care Network Heart Failure Management Application using local WiFi or cellular using the built-in GSM antenna.

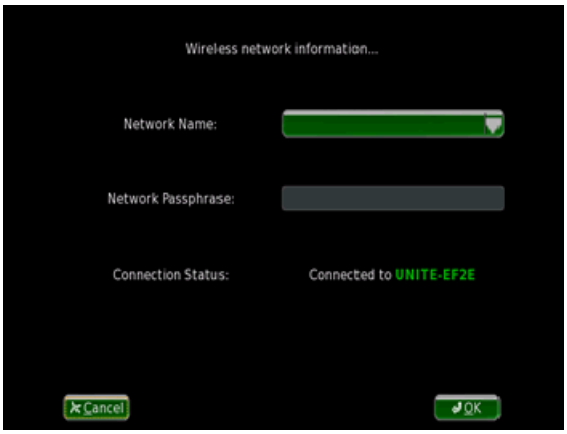
WiFi is not installed by default. Contact Customer Service to obtain the compatible WiFi accessory.

Once you have obtained the WiFi accessory, contact the IT group at your facility for credentials to your WiFi network. Some important information to consider regarding the use of WiFi by the Hospital Electronics System.

- The system only uses the WiFi network at your facility as a means to gain access to the Merlin.net Patient Care Network Heart Failure Management Application which is available on the internet.
- The system does not communicate with any other devices within your facilities' network.
- All information passed between the system and the Merlin.net Patient Care Network Heart Failure Management Application is encrypted using secure sockets (SSL).
- The system will only operate on WiFi networks that are sufficiently encrypted (WPA2). It will not operate on unprotected or open networks.
- The credentials for the WiFi network are not sent to the Merlin.net Patient Care Network Heart Failure Management Application.

Using the screen below, enable the network and then enter the network name and password.

Figure 75. WiFi Setup.

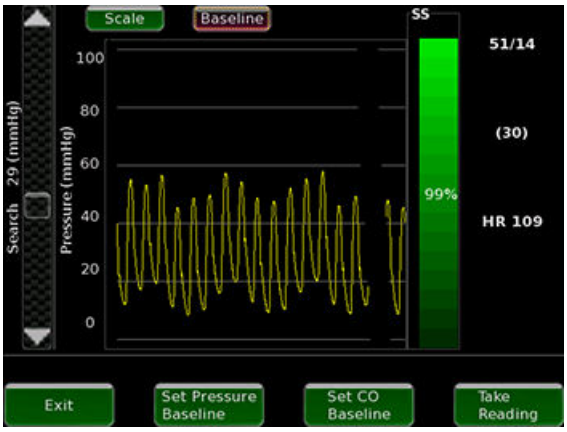


B. Setting Baseline in Follow-Up Reading

If the follow-up readings are being performed in the cardiac catheterization lab, you will be able to set the baseline to a new value.

1. Select the Baseline button at the top of the screen. This will enable the buttons used during implant to set the baselines.

Figure 76. Setting Baseline in Follow-Up.

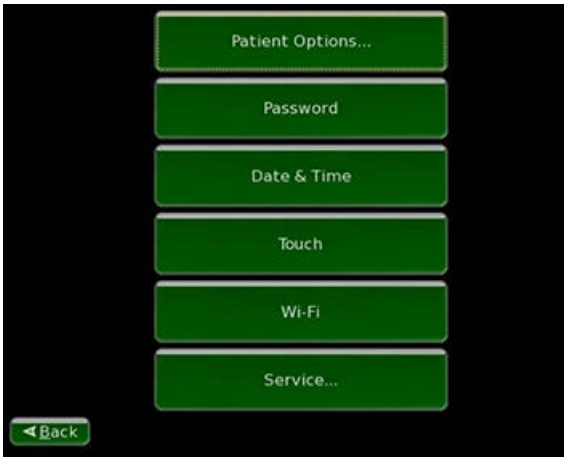


2. Select Set Pressure Baseline or Set CO Baseline to adjust baselines. Refer to the section Step 3: Set Baseline for instructions on properly setting the baseline.

If there is any change to the baseline it is important to transfer the information back to the Merlin.net Patient Care Network Heart Failure Management Application so that the system in your patient's home uses the updated baseline.

C. Settings Screen

Figure 77. Settings screen.



Patient Options…

Select the Patient Options Button to print any previously captured images, to export information from the USB flash drive for website upload, or to display baseline information for manual input into website.

Password

To change the system password or disable the password, use the Password button and follow the prompts.

Date & Time

Readings taken are identified with the Date and Time. Use this button to adjust the time on your system.

Touch

Use this option to align the touch screen.

WiFi

Select WiFi to set or update the WiFi wireless configuration. See Wireless Connectivity Setup section for details.

Service…

Provides access to service related functionality such as diagnostic test and system information.

D. The Admin Screen

The Admin screen is restricted to Merlin.net PCN administrators. If you are not a Merlin.net PCN administrator, contact your clinic administrator for help. To access the Admin screen:

1. Enter the username and password of a Merlin.net PCN administrator on the User Log On screen and then select the OK button.
2. Select the Settings button on the CardioMEMS HF screen.
   The Settings screen appears.
3. On the Settings screen, select the Service button.
4. On the Service screen, select the Admin button.

By default, new Hospital Electronics Systems require you to enter a Merlin.net PCN username and password to use the system. If your system does not require this, a Device Log On screen appears once you start the system.

If you are not a Merlin.net PCN administrator, contact your clinic administrator for help. To access the Admin screen:

1. Select the User Log On button on the Device Log On screen.
   The User Log On screen appears.
2. Enter the username and password of a Merlin.net PCN administrator and then select the OK button.
3. Select the Settings button on the CardioMEMS HF screen.
   The Settings screen appears.
4. On the Settings screen, select the Service button.
5. On the Service screen, select the Admin button.

If you are unable to gain access with the password, you can obtain a temporary password on the My Account page on the Merlin.net Patient Care Network Heart Failure Management Application. To access the system after you obtain a temporary password:

1. Enter your username and password on the User Log On Screen.
2. Select the OK button.
   The system attempts to connect to the network.
3. Select the Cancel button.
   The system logs you in.

If you are unable to log in, contact Technical Support for additional assistance.

Merlin Logon Mode

If you enable the Merlin Logon mode, users can log in to the Hospital Electronics System with their Merlin.net PCN username and password. This allows users from different clinics to share the same system.

You can only view the list of patients that are also available to your clinic on the Merlin.net Patient Care Network Heart Failure Management Application.

Remote Access

To troubleshoot an issue with your system, the Remote Access feature is available. A technician can log in to your system remotely when you enable this feature. For more information, contact Technical Support.

Software Update

Updates to the Hospital Electronics System software occur occasionally. If a network connection is available, the system automatically checks for an update after transferring the data from the first new implant or follow-up readings of the day.

If a software update is available, the system prompts you to install it:

- Select the Yes button to download and install the software.
  The update takes approximately 20 minutes depending on the network connection.
- Select the No button if you do not want to install the software.
  To update the software at any time, select the Patient Options button on the Settings screen and then select the Software Update button.

If your Hospital Electronics System does not have a network connection, software updates are installed with a USB flash drive by St. Jude Medical™.

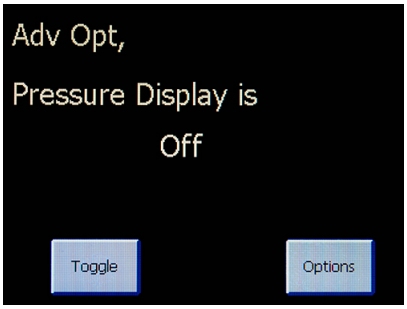
Additional Patient Electronics System Functions

Patient Electronics System - Viewing Pressure Values During the Reading

In daily use, your patient will not see their pressure values. For clinicians only, during patient training, a special clinical mode may be enabled to show the reading values. To enable this mode perform the following steps.

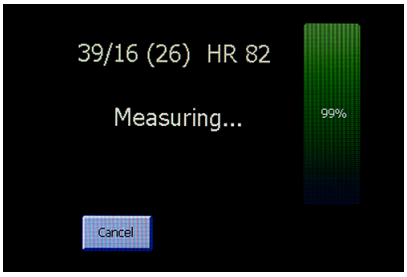
1. From the main electronics screen, select the Options button until the Advanced Options screen appears and then select the SelectAdv button.
2. Enter the Advanced Options password. This is 'sensor'. This password is reserved for clinicians. Please do not share it with your patients. If the patient ever needs to enter this screen, they can be given a daily password that is only valid for one day.
3. Select the Toggle button.

Figure 78. Enable reading values.



4. Press the round green button below the touchscreen on the handheld unit.
5. Have the patient get in position and then start the reading. During the reading, the screen will show the reading values as below.

Figure 79. Patient pressure reading with pressure values.



Guidelines for the Management of Hemodynamic Parameters

The CardioMEMS HF System allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures. Hemodynamic information obtained by the system should be used for clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

Pulmonary Artery Pressure Ranges

PA Systolic: 15 - 35 mmHg

PA Diastolic: 8 - 20 mmHg

PA Mean: 10 - 25 mmHg

Initially, thresholds will be set automatically at the acceptable range. The physician can adjust the thresholds specifically for each patient. These threshold notifications are intended to guide the physician to review the CardioMEMS HF Patient Database. Every attempt should be made to keep the pulmonary artery pressures within the specified pulmonary artery pressure ranges utilizing the guidelines. In order to clinically manage patient's PA pressures, the physician must review the PA pressure measurements on a frequent basis, for example, some patients may require a daily review of their PA pressure measurements, while some patients may need a weekly review. The physician or designee has unlimited access to the Merlin.net Patient Care Network Heart Failure Management Application.

An elevation of pressures beyond the patient's pressure ranges should be considered a volume overloaded status and should be managed according to the hyper-volemic guidelines (see Elevated PA Pressures (Hyper-volemic) section). Diuretics and vasodilators should be adjusted based on the patient's baseline diuretic requirement, knowledge of the patient's prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline.

A decrease in the pulmonary pressures below the patient's pressure ranges should be considered a volume depletion event and managed according to the hypo-volemic guideline (see Low PA Pressures (Hypo-volemic) section). Diuretic therapy should be held and the chronic dose should be lowered.

In addition to these specific guidelines, the physician should also incorporate the recommendations set forth in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [2].

The PA pressure readings should be used in addition to weights, signs and symptoms, laboratory values and other traditional markers of volume in the management of heart failure. It is important to review the trend of PA pressures. As with all other diagnostic information, physicians should consider the entire medical history of each patient when initiating or modifying therapies.

[2] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation (2022). https://doi.org/10.1161/CIR.0000000000001063

Elevated PA Pressures (Hyper-volemic)

Hyper-volemic Definitions

- Subject symptoms: Congestive symptoms (wet)
- CardioMEMS HF System Parameters: above the acceptable range
- Daily trends: elevated trend data outside the acceptable range
- Weekly trends: elevation in trend data

Treatment Recommendations

- Add or increase diuretic (and appropriate electrolyte replacement)
  - Increase or add loop diuretic
  - Change to another loop diuretic
  - Add thiazide diuretic (with caution)
  - IV doses of loop diuretic
  - Serum electrolyte evaluation with change in baseline medication
  - Re-assess pulmonary artery pressure utilizing the CardioMEMS HF System at least 2 – 3 days per week until optivolemic
- Add or increase vasodilators including long-acting nitrates
- Re-educate in salt intake and fluid restriction
- If subject has signs and symptoms of poor perfusion (cold) in addition to being hyper-volemic:
  - Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
  - Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Low PA Pressures (Hypo-volemic)

Hypo-volemic Definitions

- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- CardioMEMS HF System Parameters: below the acceptable range
- Daily trends: decrease in trend data outside the acceptable range
- Weekly trends: decrease in trend data

Treatment Recommendations

- Lower or discontinue diuretic
  - If on a thiazide diuretic with loop diuretic, lower or discontinue the dose of thiazide (and adjust electrolyte replacement)
  - If on only loop diuretic, lower the dose or discontinue
  - Consider liberalization of oral fluid restriction and salt restriction
- If postural hypotension, hold or lower vasodilators and/or oral nitrates, especially if hypotensive when sitting or supine
- If worsening renal function, hold or lower ACE/ARB dose, especially if hypotensive
- If subject had signs and symptoms of poor perfusion (cold) in addition to being hypo-volemic:
  - Consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring or the use of IV therapeutic agents
  - Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Recommended Frequency of CardioMEMS HF System Review

Subject Status	Weekly	At least 2– 3 times per week until optivolemic	At least 2 – 3 times per week until pressure stabilizes
Acceptable PA Pressure (Opti-volemic)	X		
Elevated PA Pressure (Hyper-volemic)		X	
Low PA Pressure (Hypo-volemic)		X	
Medication modifications			X
Significant deviations in trend data			X

Clinical Study Information

Introduction

Heart failure is a life-threatening condition with debilitating symptoms and is a burden to patients and their care-givers. Over 60 million people are estimated to be living with heart failure world-wide. It has been shown that pulmonary artery (PA) pressures begin to increase earlier than signs and symptoms (for example, weight gain or shortness of breath) of worsening heart failure and can provide a physiologic basis for heart failure patient management.

The CardioMEMS HF System provides a proven method for measuring PA pressure using a wireless pressure sensor implanted into the pulmonary artery. The CardioMEMS HF System provides clinicians with a patient's PA pressure while the patient is at home, without the need

for a procedure or office visit. This information allows the physician to manage the patient's heart failure proactively with the goal of controlling PA pressures and reducing heart failure hospitalizations.

GUIDE-HF Trial - Randomized Arm

The applicant performed a clinical study in the US under IDE#G170258 to establish a reasonable assurance of safety and effectiveness of the CardioMEMS HF System to guide the treatment of patients with New York Heart Association (NYHA) Class II - IV heart failure. Data from this clinical study were the basis for the current PMA supplement approval decision. A summary of the clinical study is presented below.

Study Design

Patients were enrolled from 3/15/2018 to 12/20/2019. The database for the Panel Track Supplement reflected data collected through Jan 18, 2021 and included 1007 patients from 114 U.S. sites and 15 patients at 4 sites in Canada.

The study was a prospective, randomized, controlled, single-blind, multicenter, pivotal clinical trial. The study enrolled subjects with NYHA Class II, III, or IV heart failure and either elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] or B-type natriuretic peptide [BNP]) and/or a prior HF hospitalization. All enrolled subjects underwent a right heart catheterization and implantation of a CardioMEMS device. Successfully implanted subjects were then randomized 1:1 to either hemodynamic-guided management using information provided by the CardioMEMS HF System (Treatment group) or heart failure management according to the standard of care (Control group). All patients took daily readings from home, but they were blinded to the treatment assignment or PA pressure measurements. Clinicians had access to pulmonary artery pressure information for patients in the Treatment group but not for patients in the Control group. Patient contacts were performed with scripted calls and equalized between two groups.

The study was evaluated for success based on the composite of HF hospitalization, urgent HF visits (emergency department or hospital outpatient visits for intravenous diuretic therapy), and all-cause mortality at 12 months. The study would be considered successful by demonstrating that the hemodynamic-guided HF treatment is superior to the control therapy for heart failure outcomes.

An independent Clinical Events Committee (CEC) provided blinded adjudication for all primary endpoint events. An independent Data Safety Monitoring Board (DSMB) oversaw clinical data and safety.

Clinical Inclusion and Exclusion Criteria

Enrollment in the GUIDE-HF Trial (Randomized Arm) was limited to patients who met the following inclusion criteria:

- Diagnosis and treatment for HF (regardless of LVEF) for > 90 days prior to the date of consent: subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current AHA/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, with any intolerance documented.
- NYHA Class II, III or IV HF symptoms documented within 30 days prior to consent.
- HFH within 12 months prior to consent and/or elevated NT-proBNP (or BNP) within 30 days prior to consent defined as:
  - Subjects with LVEF ≤ 40%: NT-proBNP ≥ 1000 pg/mL (or BNP ≥ 250 pg/mL).
  - Subjects with LVEF > 40%: NT-proBNP ≥ 700 pg/mL (or BNP ≥ 175 pg/mL).
  - Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) will be corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2 [3]
- ≥ 18 years of age
- Chest circumference of < 65 inches, if BMI is > 35 kg/m^2
- Written informed consent obtained from subject
- Willing and able to upload PA pressure information and comply with the follow-up requirements

Patients were not permitted to enroll in the GUIDE-HF Trial (Randomized Arm) if they met any of the following exclusion criteria:

- Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNi), and beta-blockers)
- ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
- Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 12 months
- NYHA Class IV HF patients with:
  - Continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of ≤ 4, or
  - Persistence of fluid overload with maximum (or dose equivalent) diuretic intervention
- Glomerular Filtration Rate (eGFR) < 25 mL/min and non-responsive to diuretic therapy, or receiving chronic dialysis
- Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for one month post-implantation
- Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS PA Sensor
- Implanted with mechanical right heart valve(s)
- Unrepaired severe valvular disease
- Pregnant or planning to become pregnant in the next 12 months
- An active, ongoing infection, defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum or urine).
- History of current or recurrent (≥ 2 episodes) pulmonary emboli and/or deep vein thromboses
- Major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent
- Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent
- Enrollment into another trial with an active treatment arm
- Anticipated life expectancy of < 12 months

[3] Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) were corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2 per the Frankenstein equation.

- Any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (e.g., trans-pulmonary gradient > 15) at implant RHC, a history of non-compliance, or any condition that would preclude CardioMEMS PA Sensor implantation.

Follow-up Schedule

All randomized patients were scheduled to return for follow-up examinations at 6 and 12 months. Adverse events and complications were recorded at all visits.

The key timepoints are shown in the table below summarizing schedule of treatments and evaluations.

Table 2. Schedule of Treatments and Evaluations

Trial Activity	Visit					
	Baseline (up to -60 days)	**Implant (time zero)**	**Prior to discharge**	**Phone Contact [4] (Randomized Arm Only)**	**6 months (± 14 days)**	**12 months (± 30 days)**
Informed Consent Process	X					
Assessment of Inclusion/Exclusion Criteria	X					
Demographic Information	X					
Cardiovascular History	X					
BMI (and Chest Circumference if BMI > 35kg/m^2)	X					
Limited Echo for EF (if no EF documented)	(X)					
EQ-5D-5L and KCCQ-12 Administration	X				X	X
Creatinine and Calculation of eGFR	X				X	X
NT-proBNP (or BNP)	X				X	X
Medication Review and Documentation	X		X		X	X
HF Exam (Including NYHA Assessment)	X				X	X
6MHW Test	X				X	X
CardioMEMS™ HF System Information		X				
Catheterization Laboratory PA Pressure Measurements		X				
Randomization (Randomized Arm Only [5])			X			
Subject Teaching/Compliance Assessment			X	X	X	X
Subject Contact Worksheet				X		
Medication Update Documentation		(X)	(X)	(X)	(X)	(X)
Reportable AEs	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Non-AE Device Issues		(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

(X) if applicable/as it occurs

Clinical Endpoints

With regards to effectiveness, the primary endpoint is a composite of the following:

- Hospitalization (≥ 24-hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy
- An unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit, or hospital inpatient visit and intravenous administration of diuretic therapy
- All-cause mortality

With regards to safety, the secondary safety endpoint is freedom from Device or System Related Complications (DSRCs) at 12 months post-implantation.

DSRC was defined as an adverse event that was related to or possibly related to the system (wireless pressure sensor or external electronics) and had at least one of the following characteristics:

- Treated with invasive means (other than intramuscular medication or an RHC used for diagnostic purposes)
- Resulted in the death of the subject
- Resulted in the explant of the device

[4] All sites will be required to be in contact with each subject in the Randomized Arm (including subjects in the Treatment and Control Groups) at least once every two weeks during the first three months from the date of implantation and then at least once per month from three months to the 12 month follow-up visit.

[5] Randomization should be completed as soon as possible but within 24 hours of implant, and prior to discharge.

With regard to success/failure criteria, study success was defined as demonstrating superiority for the primary endpoint hypotheses below at a significance level of 2.5%:

- H0: Hazard ratio (HR) for the Composite Endpoint at 12 months (Treatment to Control) ≥ 1
- H1: HR for the Composite Endpoint at 12 months (Treatment to Control) < 1 or
- H0: $e^{\beta 1} \geq 1$
- H1: $e^{\beta 1} < 1$

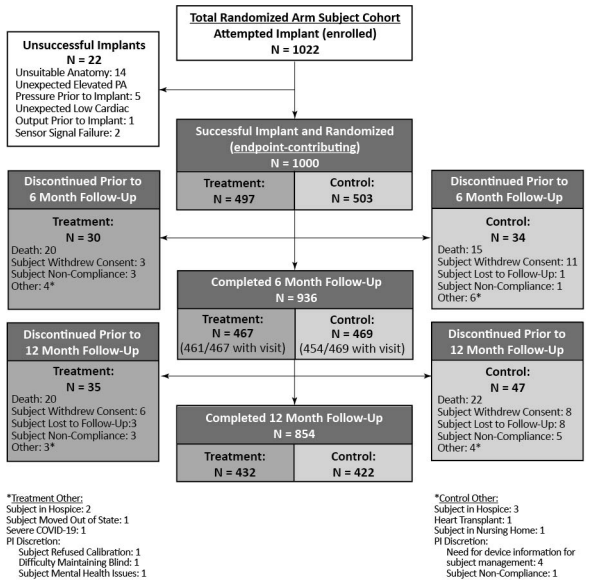
where e is the exponential function and ß1 is the regression coefficient obtained from the covariate representing randomized group (Treatment or Control) in the Andersen-Gill model. Thus, the hazard ratio is the exponentiation of the regression coefficient for randomized group. This is equivalent to testing the regression coefficient against zero.

All randomized subjects were included in the analysis population.

Accountability of the PMA Cohort

A total of 1022 patients were consented for trial enrollment and underwent a right heart catheterization and attempted implantation of a CardioMEMS device. Of these, 22 did not receive an implant, primarily due to anatomical/physiological conditions identified during the right heart catheterization. The observed PA sensor implant success rate was 97.8%. The remaining 1000 subjects who received a successful implant were randomized 1:1 to either the Treatment group (N = 497) or the Control group (N = 503). At the time of database lock, 854 (85.4%) randomized subjects completed the 12-month follow-up visit. The figure below summarizes the subject disposition in the PMA study.

Figure 80. Subject Disposition



The protocol specified the following analysis populations:

- Endpoint Analysis Population: All randomized subjects (N = 1000)
- Safety Population: All enrolled subjects (N = 1022)

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure study that enrolls NYHA Class II-IV patients in the US. The mean age was 69.2 ± 11 years and 37.5% were female. NYHA II, III, and IV patients account for 29.6%, 65.0%, and 5.4% of the randomized subjects. The table below presents the demographics and patient characteristics by randomized group. The Treatment and Control groups were balanced in all relevant demographics and baseline characteristics.

Table 3. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N = 497)	Control (N = 503)	p-value [6]
Age - year	69.2 ± 11.1 (497)	69.2 ± 11.0 (503)	0.8996
Female Sex	37.6% (187/497)	37.4% (188/503)	0.9480
Race			
▪ White	81.1% (403/497)	80.5% (405/503)	0.8725
▪ Black	17.5% (87/497)	18.5% (93/503)	0.7420
▪ Asian	0.0% (0/497)	0.2% (1/503)	1.0000
▪ American Indian or Alaskan Native	0.4% (2/497)	0.4% (2/503)	1.0000
▪ Pacific Islanders	0.0% (0/497)	0.0% (0/503)	
▪ Other	1.2% (6/497)	0.6% (3/503)	0.3389

[6] Continuous variables compared using Wilcoxon Rank Sum test, and categorical variables compared using Fisher's exact test.

Table 3. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N = 497)	Control (N = 503)	p-value
Ethnicity			
▪ Hispanic	3.2% (16/497)	3.4% (17/503)	1.0000
▪ Non-Hispanic	96.0% (477/497)	96.0% (483/503)	1.0000
▪ Unknown	0.8% (4/497)	0.6% (3/503)	0.7241
Body mass index - kg/m^2	32.9 ± 8.3 (497)	33.8 ± 8.4 (503)	0.0571
NYHA Class			
▪ II	29.4% (146/497)	29.8% (150/503)	0.8900
▪ III	64.8% (322/497)	65.2% (328/503)	0.8947
▪ IV	5.8% (29/497)	5.0% (25/503)	0.5778
Medical History			
▪ Ischemic etiology	41.6% (207/497)	37.8% (190/503)	0.2198
▪ Previous myocardial infarction	29.0% (144/497)	31.4% (158/503)	0.4093
▪ Previous percutaneous coronary intervention	33.2% (165/497)	31.4% (158/503)	0.5885
▪ Previous coronary artery bypass grafting	27.2% (135/497)	27.0% (136/503)	1.0000
▪ Diabetes	48.9% (243/497)	51.9% (261/503)	0.3759
▪ Cerebrovascular accident	13.3% (66/497)	12.9% (65/503)	0.9254
▪ Atrial flutter or fibrillation	60.4% (300/497)	57.9% (291/503)	0.4404
Vital Signs and Hemodynamic Analyses			
▪ Heart rate - bpm	73.8 ± 12.5 (497)	74.2 ± 12.3 (503)	0.7438
▪ Systolic blood pressure - mmHg	121.6 ± 19.1 (497)	120.8 ± 18.1 (503)	0.6134
▪ Diastolic blood pressure - mmHg	69.2 ± 10.8 (497)	69.0 ± 10.8 (503)	0.7996
▪ Left ventricular ejection fraction - %	39.4 ± 17.3 (497)	40.7 ± 16.9 (503)	0.1870
▪ Left ventricular ejection fraction > 40%	45.1% (224/497)	48.7% (245/503)	0.2546
▪ Pulmonary artery systolic pressure - mmHg	44.9 ± 13.9 (497)	45.2 ± 14.6 (503)	0.9194
▪ Pulmonary artery diastolic pressure - mmHg	18.9 ± 8.0 (497)	18.8 ± 7.7 (503)	0.8203
▪ Pulmonary artery mean pressure - mmHg	29.2 ± 9.5 (497)	29.4 ± 10.0 (503)	0.9631
▪ Pulmonary capillary wedge pressure - mmHg	17.3 ± 8.0 (495)	17.6 ± 7.9 (503)	0.6171
▪ Cardiac output - L/min	4.83 ± 2.62 (497)	4.70 ± 1.46 (503)	0.8459
▪ Cardiac index - L/min/m^2	2.27 ± 1.11 (497)	2.19 ± 0.63 (503)	0.4609
Ambulatory Hemodynamics during First Week			
▪ Pulmonary artery systolic pressure - mmHg	46.3 ± 14.4 (497)	46.2 ± 13.3 (499)	0.7640
▪ Pulmonary artery diastolic pressure - mmHg	22.4 ± 7.8 (497)	22.7 ± 7.4 (499)	0.4141
▪ Pulmonary artery mean pressure - mmHg	31.8 ± 10.2 (497)	31.9 ± 9.6 (499)	0.6693
▪ Heart rate - bpm	78.8 ± 11.7 (497)	79.4 ± 11.9 (499)	0.7893
Laboratory Analyses			
▪ Serum creatinine level - µmol/L	128.5 ± 44.5 (495)	133.5 ± 48.5 (495)	0.1548
▪ Estimated glomerular filtration rate - ml/min/1.73 m^2	54.3 ± 21.3 (495)	52.8 ± 20.8 (494)	0.2469
▪ B-type natriuretic peptide level - pg/mL	520.7 ± 689.2 (261)	552.4 ± 954.0 (256)	0.8499
▪ N-terminal pro-B-type natriuretic peptide level - pg/mL	2460 ± 3707 (219)	2183 ± 2803 (225)	0.5287
Treatment History			
▪ Previous cardiac resynchronization therapy	28.6% (142/497)	32.4% (163/503)	0.1926
▪ Previous implantation of defibrillator	42.9% (213/497)	40.8% (205/503)	0.5217
▪ Guideline-Directed Medical Therapy			
▪ ACE-Inhibitor or ARB or ARNi	64.2% (319/497)	63.6% (320/503)	0.8953

Table 3. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N = 497)	Control (N = 503)	p-value
▪ ARNi	29.2% (145/497)	27.6% (139/503)	0.6236
▪ Beta Blocker	89.3% (444/497)	87.9% (442/503)	0.4873
▪ Mineralocorticoid Receptor Antagonist	47.7% (237/497)	42.9% (216/503)	0.1440
▪ Diuretic	95.4% (474/497)	95.0% (478/503)	0.8827
▪ Hydralazine	16.3% (81/497)	15.9% (80/503)	0.9315
▪ Nitrate	19.9% (99/497)	20.5% (103/503)	0.8749
▪ SGLT2 Inhibitor	1.3% (2/152)	1.4% (2/140)	1.0000
Enrollment Type			
▪ Heart failure hospitalization in year prior only	34.2% (170/497)	38.0% (191/502)	0.2114
▪ Elevated natriuretic peptide level in 30 day prior only	46.3% (230/497)	42.2% (212/502)	0.2032
▪ Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.5% (97/497)	19.7% (99/502)	0.9367
KCCQ-12 at Baseline – Overall Summary Score	54.9 ± 24.3 (494)	54.9 ± 23.8 (497)	0.8876
6MHW at Baseline – m	235.2 ± 120.2 (474)	229.6 ± 123.0 (482)	0.4459

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

Safety and Effectiveness Results

Effectiveness Results

Primary Endpoint

The primary endpoint analysis was based on all randomized subjects. At 12 months, there were 253 primary endpoint events in the Treatment group compared with 289 events in the Control group. The difference between the groups represented a non-significant 12% relative risk reduction in the primary endpoint events (0.563 vs. 0.640 events per patient-year; HR 0.88, 95% CI 0.74-1.05, p=0.1624). Since the 97.5% upper confidence bound of the hazard ratio was not less than 1, the primary endpoint was not met.

The table below presents the primary endpoint analysis and the components. There were 185 heart failure hospitalizations in the treatment group and 225 in the control group (0.410 vs. 0.497 events per patient; HR 0.83, 95% CI 0.68-1.01). The rates of urgent heart failure ED/ outpatient visits or mortality were similar between the two groups.

The timing of the pivotal study overlapped with the COVID-19 pandemic. The effects of the pandemic on the study outcomes are further assessed in the sensitivity analysis section below.

Table 4. Primary Endpoint Analysis and Components

Endpoint [7]	Treatment (N = 497) Events (Rate [8])	Control (N = 503) Events (Rate [9])	Hazard Ratio (95% CI) p-value [10]
HF Hospitalization + ED/OP + Death (Primary Endpoint)	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05), p = 0.1624
HF Hospitalization + ED/OP (Secondary Endpoint)	213 (0.474)	252 (0.557)	0.85 (0.70, 1.03), p = 0.0958
HF Hospitalization	185 (0.410)	225 (0.497)	0.83 (0.68, 1.01)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	28 (0.065)	27 (0.063)	1.04 (0.61, 1.77)
Death	40 (0.094)	37 (0.086)	1.09 (0.70, 1.70)

COVID-19 Impact Sensitivity Analysis

COVID-19 Sensitivity Analysis for Interaction

The COVID-19 pandemic occurred while the pivotal study was still ongoing. Across North America, hospitals saw notable reduction in heart failure hospital admissions during COVID-19 lockdowns. Using the national emergency declaration date (March 13, 2020) in the United States as the onset date, a total of 71.7% of follow-up had been completed prior to COVID-19. The median follow-up prior to COVID-19 was 8.4 months.

The applicant added a COVID-19 impact sensitivity analysis (dated July 7, 2020) to the statistical analysis plan prior to data unblinding. The sensitivity analysis would descriptively compare the primary endpoint event rates observed during subject follow-up occurring prior to the start of the COVID-19 pandemic to rates observed during subject follow-up occurring after the start of the pandemic to evaluate impact of COVID-19, as shown in the figure below.

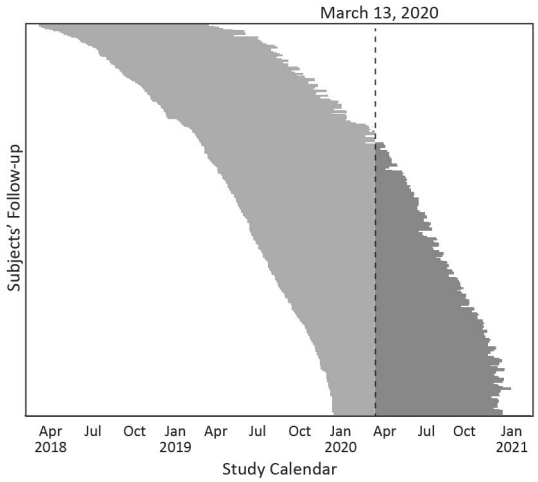
[7] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or Urgent HF Visits (HF Emergency Department/Hospital Outpatient Visits) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All-Cause Deaths are included from implant date to 395 days after implant date.

[8] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[9] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[10] Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.

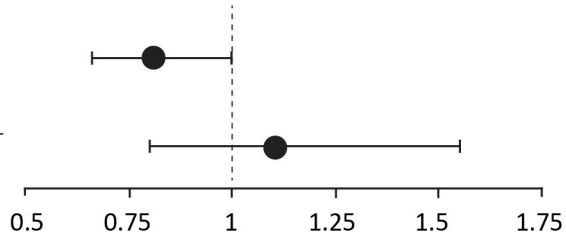
Figure 81. COVID-19 Impact Sensitivity Analysis



The sensitivity analysis demonstrated a qualitative interaction with a significant p-value of p = 0.1129 (< p = 0.15, pre-specified interaction p-value threshold), suggesting an impact of COVID-19 on the treatment effect observed in the Randomization Arm of the GUIDE-HF trial (table below). The hazard ratio for the primary endpoint events reversed from 0.81 prior to COVID-19 to 1.11 during COVID-19.

Table 5. Primary Endpoint – COVID-19 Sensitivity Analysis

Endpoint [11]	**Treatment (N = 497) Events**	**Control (N = 503) Events**	**Forest Plot**	**Hazard Ratio (95% CI)** [12]
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)				Interaction p-value [13], p = 0.1129
Prior to COVID-19 [14]	177	224		0.81 (0.66, 1.00)
During COVID-19 [15]	76	65		1.11 (0.80, 1.55)



Since the COVID-19 sensitivity analysis suggested an effect of COVID-19 on the primary endpoint, the pre-pandemic data were further explored.

Pre-COVID-19 Analysis

Pre-pandemic Primary Endpoint Events

Prior to COVID-19, there were a total of 177 primary endpoint events in the Treatment group compared with 224 events in the Control group (0.595 events vs. 0.730 events per patient, respectively). An HR of 0.81 (95% CI 0.66-1.00) for the primary endpoint, largely driven by a 27% reduction in risk for HFH, was also observed.

The results of the analysis including data prior to COVID-19 only are shown in the table below.

Table 6. Primary Endpoint Analysis and Components - Including Data Prior to COVID-19 Only

Endpoint [16]	**Treatment (N=497) Events (Rate** [17]**)**	**Control (N=503) Events (Rate** [18]**)**	**Hazard Ratio (95% CI** [19]**)**
HF Hospitalization + ED/OP + Death (Primary Endpoint)	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)

[11] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or Urgent HF Visits (HF Emergency Department/Hospital Outpatient Visits) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All-Cause Deaths are included from implant date to 395 days after implant date.

[12] Contrast Comparison Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich estimates.

[13] Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

[14] Primary Endpoint events are analyzed through March 13, 2020 for Prior to COVID-19 and analyzed after March 13, 2020 for During COVID-19.

[15] Primary Endpoint events are analyzed through March 13, 2020 for Prior to COVID-19 and analyzed after March 13, 2020 for During COVID-19.

[16] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date. Primary Endpoint events are analyzed through March 13, 2020.

[17] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[18] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[19] Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.

Table 6. Primary Endpoint Analysis and Components - Including Data Prior to COVID-19 Only

Endpoint	Treatment (N=497) Events (Rate)	Control (N=503) Events (Rate)	Hazard Ratio (95% CI)
HF Hospitalization + ED/OP (Secondary Endpoint)	147 (0.502)	199 (0.660)	0.76 (0.61, 0.95)
HF Hospitalization	124 (0.426)	176 (0.587)	0.73 (0.57, 0.92)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	23 (0.077)	23 (0.076)	1.02 (0.57, 1.82)
Death	30 (0.103)	25 (0.083)	1.24 (0.73, 2.10)

Quality of Life Assessment and Functional Assessment (6MHW)

Health status changes over time were assessed by EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire and Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at baseline, 6, and 12 months. While both Treatment and Control groups gained improvement at 6 months, there were no significant differences between the groups (table below).

The functional assessment of 6MHW distance did not show a significant improvement either within or between groups over the follow-up period.

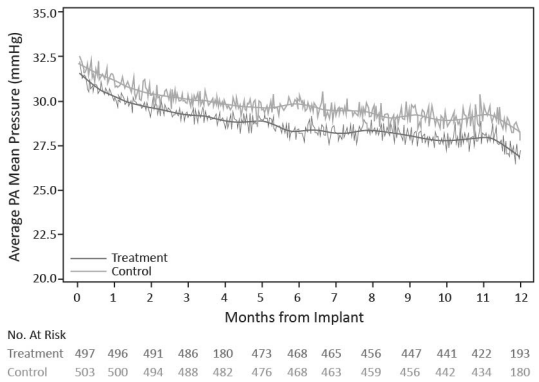
Table 7. KCCQ-12, EQ-5D-5L, and 6MHW

	6 Month Paired Change From Baseline			12 Month Paired Change from Baseline		
Component Analysis	Treatment Mean ± SD (n)	Control Mean ± SD (n)	Between Group p-value	Treatment Mean ± SD (n)	Control Mean ± SD (n)	Between Group p-value
KCCQ-12 Overall Summary Score	7.44 ± 20.68 (449)	6.14 ± 24.72 (440)	0.3545 [20]	5.20 ± 21.35 (421)	4.12 ± 22.50 (408)	0.4783 [21]
EQ-5D-5L Visual Analogue Scale	3.09 ± 19.40 (449)	3.20 ± 21.69 (441)	0.9363 [22]	0.94 ± 20,17 (421)	2.90 ± 20.71 (409)	0.1658 [23]
6MHW Test Distance	0.01 ± 87.78 (332)	2.29 ± 93.69 (342)	0.7439 [24]	-12.83 ± 100.08 (288)	-6.46 ± 106.57 (291)	0.4586 [25]

PA Pressures

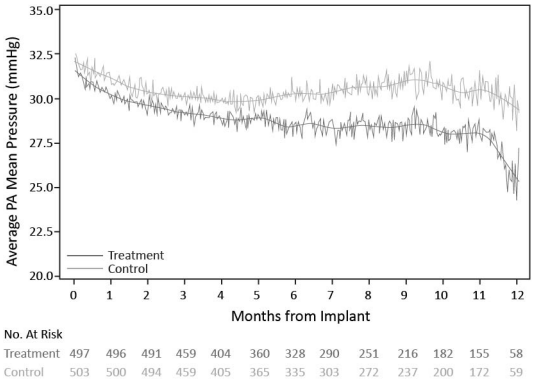
A reduction in PA mean pressure over time was observed in the Treatment group compared to Control (-2.4 ± 5.2 mmHg vs. -1.7 ± 5.0 mmHg; first figure below). A greater reduction in Treatment group PA mean pressure was also observed when limited to data prior to COVID-19 (-2.1 ± 4.8 mmHg vs. -1.4 ± 4.8 mmHg; second figure below).

Figure 82. Average PA Mean Pressure Over Time



[20] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[21] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[22] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[23] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[24] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months
[25] Student t-test comparing Treatment vs. Control change from baseline at 6 months and 12 months

Figure 83. Average PA Mean Pressure Over Time – Data Prior to COVID-19 Only



Safety Results

Freedom from Device or System Related Complications (DSRC)

A total of 8 DSRC events occurred in 8 subjects in the safety population. The observed rate of freedom from Device or System Related Complications was 99.2% (1014/1022). None of the 8 DSRCs resulted in death or explant of the device, and most were vascular injury events due to vascular access or device implant. The table below presents a summary of DSRCs.

Table 8. Summary of DSRCs as Adjudicated by the CEC (Safety Population)

			DSRC Criteria Met		
Cohort System Organ Class Preferred Term	**Number of DSRCs**	**Proportion of Subjects with DSRCs**	**Treated with Invasive Means**	**Resulted in Death**	**Resulted in Device Explant**
Safety Population (N = 1022)					
General Disorders and Administration Site Conditions	5	0.49% (5/1022)	5	0	0
▪ Catheter Site Hematoma	1	0.10% (1/1022)	1	0	0
▪ Catheter Site Hemorrhage	2	0.20% (2/1022)	2	0	0
▪ Device Dislocation	1	0.10% (1/1022)	1	0	0
▪ Device Malfunction	1	0.10% (1/1022)	1	0	0
Injury, Poisoning and Procedural Complications	3	0.29% (3/1022)	3	0	0
▪ Arterial Injury	2	0.20% (2/1022)	2	0	0
▪ Vascular Pseudoaneurysm	1	0.10% (1/1022)	1	0	0
Total	8	0.78% (8/1022)	8	0	0

Hospitalizations

The table below summarizes the all-cause hospitalizations reported during the 12-month follow-up for all randomized subjects. Treatment group experienced a lower all-cause hospitalizations rate comparing to the Control group (468 vs. 492) though similar proportion of subjects in each group had at least one hospitalization during the study.

Table 9. Summary of Hospitalizations as Adjudicated by the CEC (Endpoint Analysis Population)

	Treatment (N = 497)		Control (N= 503)	
Adjudicated Cause	**Count [Rate [26]]**	**Percent of Subjects with Event**	**Count [Rate [27]]**	**Percent of Subjects with Event**
Worsening heart failure	233 [50.3]	27.4% (136/497)	269 [57.7]	30.4% (153/503)
▪ HF Hospitalization	185 [39.9]	24.1% (120/497)	225 [48.2]	27.6% (139/503)
▪ Urgent HF Visit	28 [6.04]	4.4% (22/497)	27 [5.79]	5.0% (25/503)
▪ Not a Protocol Defined HF Admission	20 [4.32]	3.4% (17/497)	17 [3.65]	3.0% (15/503)
Other cardiovascular	200 [43.2]	27.4% (136/497)	186 [39.9]	25.0% (126/503)
▪ CABG	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Myocardial Infarction or Other Forms of Ischemic Heart Disease	26 [5.61]	4.0% (20/497)	46 [9.86]	7.6% (38/503)
▪ Product Issue [28]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

[26] Rate is number of events per 100 subject years.
[27] Rate is number of events per 100 subject years.
[28] Hospitalization due to events related to the device.

Table 9. Summary of Hospitalizations as Adjudicated by the CEC (Endpoint Analysis Population)

	Treatment (N = 497)		Control (N= 503)	
Adjudicated Cause	**Count [Rate]**	**Percent of Subjects with Event**	**Count [Rate]**	**Percent of Subjects with Event**
▪ Thrombosis or Thromboembolism	12 [2.59]	2.0% (10/497)	6 [1.29]	1.2% (6/503)
▪ Valve Surgery	5 [1.08]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
▪ Ventricular or Atrial Arrhythmia	57 [12.3]	9.1% (45/497)	55 [11.8]	8.5% (43/503)
▪ Other	99 [21.4]	14.7% (73/497)	72 [15.4]	11.9% (60/503)
Non-cardiovascular	35 [7.55]	6.8% (34/497)	37 [7.93]	6.4% (32/503)
Total	468 [101.0]	47.1% (234/497)	492 [105.5]	46.5% (234/503)

Mortality

A total of 77 subjects died in the study. There were 40 (0.094) all-cause deaths in the Treatment group and 37 (0.086) all-cause deaths in the Control group. The table below presents the causes of deaths between the two groups per CEC adjudication.

Table 10. Summary of Deaths as Adjudicated by the CEC (Endpoint Analysis Population)

Adjudicated Cause	**Treatment (N = 497)**	**Control (N = 503)**
Cardiovascular	6.0% (30/497)	4.8% (24/503)
▪ Cardiovascular procedure	0.2% (1/497)	0.0% (0/503)
▪ Heart failure	3.4% (17/497)	3.0% (15/503)
▪ Sudden cardiac death	2.2% (11/497)	1.8% (9/503)
▪ Other	0.2% (1/497)	0.0% (0/503)
Non-cardiovascular	1.6% (8/497)	2.6% (13/503)
▪ Gastrointestinal	0.0% (0/497)	0.2% (1/503)
▪ Hemorrhage	0.0% (0/497)	0.2% (1/503)
▪ Infection	0.6% (3/497)	0.6% (3/503)
▪ Inflammatory, Immune (including autoimmune)	0.0% (0/497)	0.2% (1/503)
▪ Neurological	0.2% (1/497)	0.2% (1/503)
▪ Pulmonary	0.2% (1/497)	0.4% (2/503)
▪ Renal	0.4% (2/497)	0.4% (2/503)
▪ Other non-cardiovascular	0.2% (1/497)	0.4% (2/503)
Undetermined cause of death	0.4% (2/497)	0.0% (0/503)
Total	8.0% (40/497)	7.4% (37/503)

There were no device-related deaths.

Two subjects died within 30 days after the procedure. A patient with ischemic cardiomyopathy, atrial fibrillation and a history of valvular heart disease status post TAVR developed abdominal pain post-operatively. The patient was found to have ischemic bowel and died on post-operative day 2. The death was adjudicated as procedure-related but not device-related. Another patient died of sudden cardiac arrest on day 29 after the procedure. CEC adjudicated the death as not device- or procedure-related.

Adverse Events

The first table below presents a summary of adverse events as reported by investigators. There were no unanticipated adverse device effects. The second and third tables below present the serious and non-serious adverse device effects reported in the pivotal study.

Table 11. Summary of Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N= 503)	
Adverse Event Class	**Events [Rate [29]]**	**Percent of Subjects with Event**	**Events [Rate [30]]**	**Percent of Subjects with Event**
SAE	729 [157.3]	56.7% (282/497)	799 [171.3]	53.3% (268/503)
ADE	16 [3.45]	3.0% (15/497)	20 [4.29]	4.0% (20/503)
SADE	9 [1.94]	1.8% (9/497)	15 [3.22]	2.4% (12/503)
UADE	0 [0.00]	0.0% (0/497)	0 [0.00]	0.0% (0/503)

[29] Rate is number of events per 100 subject years.
[30] Rate is number of events per 100 subject years.

Table 12. Summary of Serious Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N = 497)		Control (N = 503)	
	Events [Rate [31]]	Percent of Subjects with Event	Events [Rate [32]]	Percent of Subjects with Event
Overall Follow-up				
Cardiac Disorders	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Arrhythmia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Cardiac Failure Congestive	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
General Disorders and Administration Site Conditions [33]	4 [0.86]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
▪ Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	1 [0.21]	0.2% (1/503)
▪ Device Deployment Issue [34]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Device Dislocation [35]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Arterial Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	0 [0.00]	0.0% (0/497)	6 [1.29]	1.0% (5/503)
▪ Hemoptysis	0 [0.00]	0.0% (0/497)	4 [0.86]	0.6% (3/503)
▪ Pulmonary Embolism	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Vascular Disorders	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
▪ Embolism	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Hematoma	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Thrombosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	9 [1.94]	1.8% (9/497)	15 [3.22]	2.4% (12/503)

Table 13. Summary of Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N = 497)		Control (N = 503)	
	Events [Rate [36]]	Percent of Subjects with Event	Events [Rate [37]]	Percent of Subjects with Event
Cardiac Disorders	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
▪ Arrhythmia	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
General Disorders and Administration Site Conditions	9 [1.94]	1.8% (9/497)	18 [3.86]	3.6% (18/503)
▪ Catheter Site Hematoma	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
▪ Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
▪ Device Deployment Issue	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Device Dislocation	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
▪ Device Information Output Issue	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
▪ Device Malfunction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Pyrexia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Vessel Puncture Site Pain	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Arterial Injury	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

[31] Rate is number of events per 100 subject years.
[32] Rate is number of events per 100 subject years.
[33] Administration Site Conditions refers to events associated with site at which the device is administered.
[34] Device did not completely detach from delivery catheter upon initial deployment, but was ultimately deployed and confirmed to be working successfully.
[35] Partial dislodgement of a left ventricular pacemaker lead during the CardioMEMS device implantation procedure, requiring subsequent lead revision. All SADEs occurred in NYHA Class II/III subjects prior to COVID-19.
[36] Rate is number of events per 100 subject years.
[37] Rate is number of events per 100 subject years.

Table 13. Summary of Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N = 497)		Control (N = 503)	
	Events [Rate]	Percent of Subjects with Event	Events [Rate]	Percent of Subjects with Event
▪ Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Nervous System Disorders	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Presyncope	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Respiratory, Thoracic and Mediastinal Disorders	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
▪ Hemoptysis	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Vascular Disorders	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hypotension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	16 [3.45]	3.0% (15/497)	20 [4.29]	4.0% (20/503)

All ADEs occurred in NYHA Class II/III subjects prior to COVID-19.

Serious Adverse Events

A serious adverse event (SAE) was defined as an adverse event not related to the use of the device but meeting seriousness criteria (requiring hospitalization or invasive intervention or resulting in a life-threatening illness or injury). A summary of non-device-related investigator-reported SAEs is provided in the table below.

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N = 497)		Control (N = 503)	
	Events [Rate [38]]	Percent of Subjects with Event	Events [Rate [39]]	Percent of Subjects with Event
Blood and Lymphatic System Disorders	11 [2.37]	1.6% (8/497)	8 [1.72]	1.4% (7/503)
▪ Anemia	9 [1.94]	1.2% (6/497)	8 [1.72]	1.4% (7/503)
▪ Thrombocytopenia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Cardiac Disorders	302 [65.2]	32.6% (162/497)	389 [83.4]	38.8% (195/503)
▪ Acute Myocardial Infarction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Angina Pectoris	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Angina Unstable	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Aortic Valve Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Arrhythmia	53 [11.4]	9.5% (47/497)	54 [11.6]	9.1% (46/503)
▪ Atrioventricular Block Complete	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cardiac Aneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cardiac Arrest	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
▪ Cardiac Failure Congestive	216 [46.6]	26.2% (130/497)	276 [59.2]	30.8% (155/503)
▪ Cardiac Perforation	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cardiac Valve Disease	1 [0.22]	0.2% (1/497)	4 [0.86]	0.6% (3/503)
▪ Cardiogenic Shock	8 [1.73]	1.6% (8/497)	6 [1.29]	1.0% (5/503)
▪ Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Coronary Artery Disease	1 [0.22]	0.2% (1/497)	9 [1.93]	1.6% (8/503)
▪ Intracardiac Thrombus	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Ischemic Cardiomyopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Mitral Valve Disease	1 [0.22]	0.2% (1/497)	3 [0.64]	0.4% (2/503)
▪ Mitral Valve Incompetence	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Myocardial Infarction	11 [2.37]	2.0% (10/497)	16 [3.43]	3.2% (16/503)
▪ Pericardial Effusion	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
▪ Pericarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Prinzmetal Angina	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)

[38] Rate is number of events per 100 subject years.
[39] Rate is number of events per 100 subject years.

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N = 503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
▪ Restrictive Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Tachycardia	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Ear and Labyrinth Disorders	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Vertigo	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Vertigo Positional	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Endocrine Disorders	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Hypothyroidism	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Inappropriate Antidiuretic Hormone Secretion	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastrointestinal Disorders	29 [6.26]	4.8% (24/497)	33 [7.08]	5.0% (25/503)
▪ Abdominal Pain	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
▪ Colitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Colitis Ischemic	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Colonic Stenosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Constipation	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
▪ Diarrhea	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
▪ Duodenal Ulcer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Dysphagia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Gastritis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Gastrointestinal Hemorrhage	10 [2.16]	1.8% (9/497)	20 [4.29]	3.2% (16/503)
▪ Gastrointestinal Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Gastroesophageal Reflux Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hemorrhoidal Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Ileus	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Impaired Gastric Emptying	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Intestinal Ischemia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Nausea	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Pancreatic Mass	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Pancreatitis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Pancreatitis Acute	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Proctitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Small Intestinal Obstruction	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Spigelian Hernia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Vomiting	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
General Disorders and Administration Site Conditions [40]	49 [10.6]	8.2% (41/497)	34 [7.29]	6.2% (31/503)
▪ Accidental Death [41]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Asthenia	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
▪ Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Chest Pain	32 [6.90]	5.4% (27/497)	25 [5.36]	4.6% (23/503)
▪ Death [42]	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
▪ Device Dislocation [43]	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Device Electrical Impedance Issue [44]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

[40] Administration Site Conditions refers to events associated with site at which the device is administered.
[41] Traumatic death in an accident.
[42] Unknown event leading to death.
[43] Hip prosthesis dislocation, unrelated to study device.

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N = 503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
▪ Device Malfunction [45]	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
▪ Fatigue	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Generalized Edema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hypothermia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Implant Site Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Multi-Organ Failure	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Polyp	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Sudden Cardiac Death [46]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hepatobiliary Disorders	4 [0.86]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
▪ Cholangitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cholelithiasis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hepatic Cirrhosis	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
▪ Hepatic Function Abnormal	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Ischemic Hepatitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Immune System Disorders	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
▪ Drug Hypersensitivity	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Heart Transplant Rejection	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Infections and Infestations	99 [21.4]	15.3% (76/497)	113 [24.2]	16.9% (85/503)
▪ Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Anal Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Bronchitis	2 [0.43]	0.4% (2/497)	7 [1.50]	1.4% (7/503)
▪ Cellulitis	6 [1.29]	1.0% (5/497)	8 [1.72]	1.4% (7/503)
▪ Central Nervous System Abscess	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Clostridial Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Coronavirus Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Cystitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Endocarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Gastroenteritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Gastroenteritis Viral	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Gastrointestinal Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Herpes Zoster	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Infection	29 [6.26]	5.4% (27/497)	39 [8.36]	6.8% (34/503)
▪ Influenza	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
▪ Intervertebral Discitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Mycotic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Pneumonia	27 [5.83]	4.8% (24/497)	32 [6.86]	5.8% (29/503)
▪ Sepsis	18 [3.88]	3.4% (17/497)	10 [2.14]	2.0% (10/503)
▪ Septic Shock	0 [0.00]	0.0% (0/497)	4 [0.86]	0.8% (4/503)
▪ Upper Respiratory Tract Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Urinary Tract Infection	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
▪ Wound Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

[44] Broken pacemaker lead, unrelated to study device.
[45] Cardiac pacemaker or ICD malfunction, unrelated to study device.
[46] Sudden cardiac death due to ischemic heart disease.

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N = 503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Injury, Poisoning and Procedural Complications	15 [3.24]	2.8% (14/497)	16 [3.43]	3.0% (15/503)
▪ Cervical Vertebral Fracture	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Fall	4 [0.86]	0.8% (4/497)	6 [1.29]	1.0% (5/503)
▪ Femur Fracture	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hip Fracture	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
▪ Iliotibial Band Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Joint Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Multiple Fractures	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Pelvic Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Road Traffic Accident [47]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Spinal Compression Fracture	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Spinal Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Subdural Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Investigations	21 [4.53]	3.8% (19/497)	21 [4.50]	3.0% (15/503)
▪ Anticoagulation Drug Level Below Therapeutic	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Blood Creatinine Increased	18 [3.88]	3.4% (17/497)	17 [3.65]	2.6% (13/503)
▪ International Normalized Ratio Decreased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ International Normalized Ratio Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Left Ventricular End-Diastolic Pressure Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Transaminases Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Troponin Increased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Metabolism and Nutrition Disorders	25 [5.39]	4.8% (24/497)	24 [5.15]	4.0% (20/503)
▪ Dehydration	8 [1.73]	1.6% (8/497)	2 [0.43]	0.4% (2/503)
▪ Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Diabetic Ketoacidosis	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
▪ Fluid Overload	2 [0.43]	0.4% (2/497)	2 [0.43]	0.2% (1/503)
▪ Gout	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
▪ Hyperglycemia	5 [1.08]	1.0% (5/497)	5 [1.07]	0.8% (4/503)
▪ Hyperkalemia	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Hypoglycemia	2 [0.43]	0.4% (2/497)	4 [0.86]	0.8% (4/503)
▪ Hypokalemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
▪ Hypovolemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
▪ Lactic Acidosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Type 2 Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Musculoskeletal and Connective Tissue Disorders	14 [3.02]	2.4% (12/497)	4 [0.86]	0.8% (4/503)
▪ Arthralgia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Back Pain	5 [1.08]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
▪ Compartment Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Fibromyalgia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Muscular Weakness	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Myopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

[47] Multiple injuries and surgical procedures resulting from a motor vehicle accident.

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N = 503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
▪ Osteoarthritis	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
▪ Rhabdomyolysis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Rheumatoid Arthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Spinal Osteoarthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
▪ Colon Cancer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Lung Neoplasm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Esophageal Adenocarcinoma	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Squamous Cell Carcinoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nervous System Disorders	42 [9.06]	7.4% (37/497)	28 [6.00]	4.8% (24/503)
▪ Carotid Artery Stenosis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Cerebrovascular Accident	12 [2.59]	2.2% (11/497)	6 [1.29]	1.2% (6/503)
▪ Cerebrovascular Disorder	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cervicogenic Headache	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ CNS Ventriculitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Complicated Migraine	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Convulsion	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Dizziness	4 [0.86]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
▪ Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Hemorrhage Intracranial	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Headache	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hepatic Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Hypoesthesia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Metabolic Encephalopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Myoclonus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Partial Seizures	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Presyncope	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
▪ Sciatica	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Subarachnoid Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Syncope	12 [2.59]	2.4% (12/497)	8 [1.72]	1.6% (8/503)
▪ Transient Ischemic Attack	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Vertebral Artery Stenosis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Psychiatric Disorders	3 [0.65]	0.6% (3/497)	6 [1.29]	1.0% (5/503)
▪ Depression	0 [0.00]	0.0% (0/497)	3 [0.64]	0.4% (2/503)
▪ Mental Disorder	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Mental Status Changes	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Renal and Urinary Disorders	29 [6.26]	4.8% (24/497)	41 [8.79]	7.6% (38/503)
▪ Hematuria	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Nephrolithiasis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Obstructive Uropathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Renal Failure	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
▪ Renal Failure Acute	21 [4.53]	3.6% (18/497)	29 [6.22]	5.6% (28/503)
▪ Renal Failure Chronic	2 [0.43]	0.4% (2/497)	6 [1.29]	1.0% (5/503)

Table 14. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N = 497)		Control (N = 503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
▪ Urinary Retention	3 [0.65]	0.6% (3/497)	2 [0.43]	0.4% (2/503)
Reproductive System and Breast Disorders	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Benign Prostatic Hyperplasia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Vaginal Hemorrhage	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	42 [9.06]	6.8% (34/497)	52 [11.2]	7.6% (38/503)
▪ Acute Respiratory Failure	3 [0.65]	0.6% (3/497)	8 [1.72]	1.6% (8/503)
▪ Asthma	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Chronic Obstructive Pulmonary Disease	13 [2.80]	1.8% (9/497)	24 [5.15]	2.8% (14/503)
▪ Chronic Respiratory Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cough	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Dyspnea	7 [1.51]	1.4% (7/497)	8 [1.72]	1.6% (8/503)
▪ Epistaxis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Hemoptysis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Hypoxia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Pleural Effusion	5 [1.08]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
▪ Pneumothorax	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Pulmonary Alveolar Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Pulmonary Embolism	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
▪ Pulmonary Hypertension	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Respiratory Failure	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
▪ Sleep Apnea Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Skin and Subcutaneous Tissue Disorders	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Angioedema	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hyperhidrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Surgical and Medical Procedures	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
▪ Cardiac Pacemaker Replacement	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Vascular Disorders	35 [7.55]	5.0% (25/497)	20 [4.29]	3.6% (18/503)
▪ Aortic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Bleeding Varicose Vein	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Embolism	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Extremity Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
▪ Hypertension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Hypertensive Crisis	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Hypotension	14 [3.02]	2.6% (13/497)	11 [2.36]	2.2% (11/503)
▪ Lymphoedema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Orthostatic Hypotension	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
▪ Peripheral Arterial Occlusive Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Shock	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
▪ Thrombosis	5 [1.08]	0.8% (4/497)	3 [0.64]	0.4% (2/503)
Total	729 [157.3]	56.7% (282/497)	799 [171.3]	53.3% (268/503)

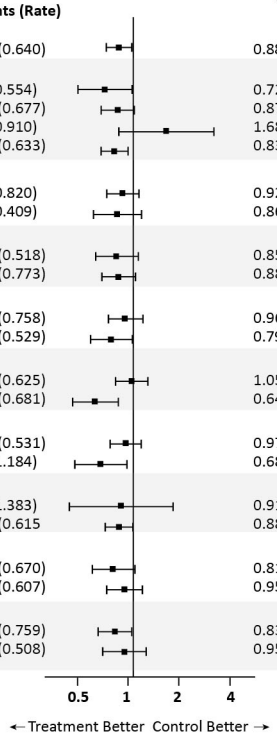
Subgroup Analyses

The primary endpoint was evaluated in subgroups of NYHA Class, qualifying category, ejection fraction, age, sex, race, ethnicity, ischemic cardiomyopathy, and prior cardiac device implant. The figures below show the forest plots for all follow-up and pre-COVID-19, respectively. Women notably derived more benefit than men with 36% reduction in primary endpoint events. African American subjects also gained a

larger treatment effect, though minorities (African American and Hispanic subjects) in both the Treatment group and the Control group experienced high rates of primary endpoint events.

Table 15. Subgroup Analyses – All Follow-up

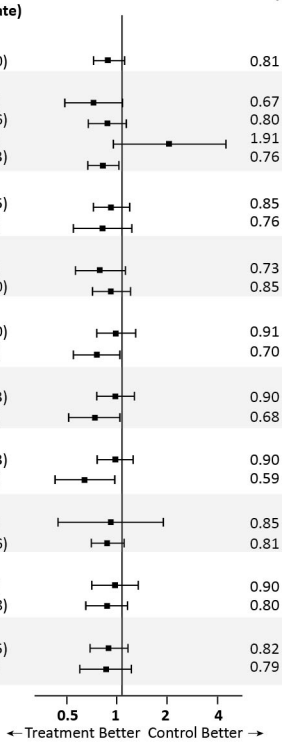
Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Subgroup p-value	Interaction p-value
Overal	1000	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05)	0.16	
NYHA Class						
NYHA Class II	296	53 (0.401)	75 (0.554)	0.72 (0.50, 1.05)	0.086	0.095
NYHA Class III*	650	171 (0.589)	198 (0.677)	0.87 (0.70, 108)	0.21	
NYHA Class IV	54	29 (1.527)	16 (0.910)	1.68 (0.88, 3.20)	0.12	
NYHA Class II and III	946	224 (0.525)	273 (0.633)	0.83 (0.69. 1.00)	0.050	0.046†
Qualification						
HFH in year prior	557	181 (0.757)	33 (0.820)	0.92 (0.74, 1.14)	0.47	0.71
Elevated BNP/NT pro-BNP only	442	72 (0.350)	77 (0.409)	0.86 (0.62, 1.19)	0.36	
Ejection Fraction						
HFpEF (EF>40%)*	469	90 (0.442)	114 (0.518)	0.85 (0.64, 1.14)	0.28	0.90
HFrEF (EF≤40%)*	531	163 (0.677)	175 (0.773)	0.88 (0.70, 1.10)	0.26	
Age						
Below Median (<71 Years)*	492	156 (0.730)	173 (0.758)	0.96 (0.76, 1.22)	0.75	0.30
Median and Above (≥71 Years)*	508	97 (0.420)	116 (0.529)	0.79 (0.60, 1.05)	0.11	
Sex						
Men*	625	178 (0.656)	171 (0.625)	1.05 (0.84, 1.31)	0.67	0.010
Women*	375	75 (0.434)	118 (0.681)	0.64 (0.47, 0.87)	0.004	
Race						
Caucasian*	807	189 (0.516)	194 (0.531)	0.97 (0.79, 1.20)	0.78	0.095
African American*	179	60 (0.811)	94 (1.184)	0.68 (0.48, 0.97)	0.035	
Ethnicity						
Hispanic*	33	18 (1.257)	21 (1.383)	0.91 (0.45, 183)	0.79	0.95
Non-Hispanic*	960	232 (0.544)	264 (0.615	0.88 (0.73, 1.07)	0.20	
Ischemic Cardiomiopathy						
Ischemic*	397	99 (0.545)	112 (0.670)	0.81 (0.61, 1.08)	0.16	0.40
Non-Ischemic*	560	142 (0.578)	160 (0.607)	0.95 (0.75, 1.21)	0.69	
Device Implant						
With CRT-D/CRT-P/ICD*	562	162 (0.633)	188 (0.759)	0.83 (0.67, 1.04)	0.11	0.48
Without CRT-D/CRT-P/ICD*	438	91 (0.482)	101 (0.508)	0.95 (0.71, 1.28)	0.73	



*Pre-specified subgroup
†Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Table 16. Subgroup Analyses – Prior to COVID-19

Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Interaction p-value
Overall	1000	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)	
NYHA Class					
NYHA Class II	296	43 (0.393)	70 (0.591)	0.67 (0.45, 0.99)	0.074
NYHA Class III	650	114 (0.552)	141 (0.686)	0.80 (0.62, 1.04)	
NYHA Class IV	54	20 (3.123)	13 (1.632)	1.91 (0.88, 4.18)	
NYHA Class II and III	946	157 (0.497)	211 (0.653)	0.76 (0.61, 0.95)	0.035*
Qualification					
HFH in year prior	557	133 (0.771)	166 (0.905)	0.85 (0.67, 1.09)	0.58
Elevated BNP/NT pro-BNP only	442	44 (0.358)	58 (0.474)	0.76 (0.51, 1.13)	
Ejection Fraction					
HFpEF (EF>40%)	469	57 (0.401)	85 (0.551)	0.73 (0.51, 1.03)	0.50
HFrEF (EF≤40%)	531	120 (0.738)	139 (0.870)	0.85 (0.65, 1.10)	
Age					
Below Median (<71 Years)	492	112 (0.746)	130 (0.820)	0.91 (0.69, 1.19)	0.22
Median and Above (≥71 Years)	508	65 (0.442)	94 (0.635)	0.70 (0.50, 0.97)	
Sex					
Men*	625	121 (0.687)	139 (0.763)	0.90 (0.70, 1.17)	0.21
Women*	375	56 (0.462)	85 (0.683)	0.68 (0.48, 0.96)	
Race					
White*	807	135 (0.607)	154 (0.673)	0.90 (0.71, 1.15)	0.091
Black*	179	38 (0.721)	70 (1.221)	0.59 (0.39, 0.89)	
Ethnicity					
Hispanic*	33	17 (1.575)	19 (1.860)	0.85 (0.41, 1.76)	0.84
Non-Hispanic*	960	157 (0.586)	202 (0.726)	0.81 (0.65, 1.01)	
Ischemic Cardiomiopathy					
Ischemic*	397	83 (0.682)	87 (0.760)	0.90 (0.65, 1.24)	0.61
Non-Ischemic*	560	91 (0.526)	125 (0.658)	0.80 (0.60, 1.06)	
Device Implant					
With CRT-D/CRT-P/ICD	562	117 (0.776)	144 (0.945)	0.82 (0.63, 1.06)	0.92
Without CRT-D/CRT-P/ICD	438	60 (0.424)	80 (0.535)	0.79 (0.56, 1.12)	



*Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Within the subgroup analyses, an interaction was observed for NYHA class, with the subgroup of NYHA Class IV patients (N = 54) demonstrating a different treatment effect than NYHA Class II and/or III patients. NYHA Class II/III patients overall demonstrated a 24% reduction in primary endpoint events prior to COVID-19 (HR 0.76, 95% CI 0.61-0.95) while NYHA Class IV patients did worse with

hemodynamic-guided HF therapy during the same period (HR 1.91, CI 0.88-4.18). The NYHA Class sensitivity analysis demonstrated an interaction p-value of p = 0.035, and separate analysis for each NYHA Class is provided below.

NYHA Class II

The baseline demographics and key characteristics for the NYHA Class II patients in the Treatment group and the Control group were balanced and listed in the table below.

Table 17. Demographics and Baseline Assessments – NYHA Class II Subjects

	Treatment (N = 146)	**Control (N = 150)**
Age - yr	69.8 ± 10.9 (146)	69.8 ± 10.5 (150)
Female Sex	33.6% (49/146)	34.0% (51/150)
Race		
▪ White	84.2% (123/146)	82.0% (123/150)
▪ Black	15.1% (22/146)	17.3% (26/150)
▪ Other	0.7% (1/146)	0.7% (1/150)
Ethnicity		
▪ Hispanic	2.7% (4/146)	4.0% (6/150)
▪ Non-Hispanic	95.2% (139/146)	96.0% (144/150)
▪ Unknown	2.1% (3/146)	0.0% (0/150)
Body mass index - kg/m^2	30.7 ± 7.3 (146)	32.5 ± 7.4 (150)
Medical History		
▪ Ischemic etiology	43.2% (63/146)	45.3% (68/150)
▪ Diabetes	49.3% (72/146)	44.7% (67/150)
▪ Atrial flutter or fibrillation	56.8% (83/146)	58.0% (87/150)
Vital Signs and Hemodynamic Analyses		
▪ Left ventricular ejection fraction - %	39.2 ± 17.2 (146)	39.8 ± 16.1 (150)
▪ Left ventricular ejection fraction > 40%	42.5% (62/146)	44.0% (66/150)
▪ Pulmonary capillary wedge pressure - mmHg	16.9 ± 8.2 (145)	17.7 ± 8.4 (150)
▪ Cardiac output - L/min	4.61 ± 1.30 (146)	4.51 ± 1.10 (150)
▪ Cardiac index - L/min/m^2	2.27 ± 0.61 (146)	2.14 ± 0.48 (150)
Laboratory Analyses		
▪ Serum creatinine level - µmol/L	123.1 ± 40.7 (146)	128.3 ± 44.7 (144)
▪ Estimated glomerular filtration rate - ml/min/ 1.73m^2	56.7 ± 21.5 (146)	54.6 ± 19.2 (143)
▪ B-type natriuretic peptide level - pg/mL	472.8 v 480.3 (61)	525.4 ± 727.7 (69)
▪ N-terminal pro-B-type natriuretic peptide level - pg/mL	2526 ± 3842 (76)	1537 ± 985 (72)
Treatment History		
▪ Previous cardiac resynchronization therapy	26.7% (39/146)	35.3% (53/150)
▪ Previous implantation of defibrillator	49.3% (72/146)	40.0% (60/150)
▪ Guideline-Directed Medical Therapy		
▪ ACE-Inhibitor or ARB or ARNi	69.2% (101/146)	70.0% (105/150)
▪ ARNi	32.9% (48/146)	30.0% (45/150)
▪ Beta Blocker	89.7% (131/146)	91.3% (137/150)
▪ Mineralocorticoid Receptor Antagonist	43.2% (63/146)	33.3% (50/150)
▪ Diuretic	90.4% (132/146)	93.3% (140/150)
▪ Hydralazine	11.6% (17/146)	20.0% (30/150)
▪ Nitrate	17.8% (26/146)	16.7% (25/150)
▪ SGLT2 Inhibitor	2.2% (1/46)	0.0% (0/41)
Enrollment Type		
▪ Heart failure hospitalization in year prior only	32.2% (47/146)	32.7% (49/150)

Table 17. Demographics and Baseline Assessments – NYHA Class II Subjects

	Treatment (N = 146)	Control (N = 150)
▪ Elevated natriuretic peptide level in 30 day prior only	50.7% (74/146)	49.3% (74/150)
▪ Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	17.1% (25/146)	18.0% (27/150)
Patient Reported Outcomes		
▪ KCCQ-12 at Baseline - Overall Summary Score	69.7 ± 20.7 (145)	66.4 ± 20.5 (147)
▪ 6MHW as Baseline - m	285.5 ± 111.3 (142)	264.8 ± 120.3 (146)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

The primary endpoint event rates and components for NYHA Class II subjects for the full follow-up and prior to COVID-19 are presented in the table below. Before the pandemic, there were 43 primary endpoint events in the Treatment group compared with 70 events in the Control group, representing a 33% reduction in the 12-month rate of primary endpoint events (0.393 events per patient in the Treatment group vs. 0.591 events per patient in the Control group, HR 0.67).

Table 18. Primary Endpoint and Components – NYHA Class II Subjects

Endpoint [48]	**Treatment (N = 146) Events (Rate [49])**	**Control (N = 150) Events (Rate [50])**	**Hazard Ratio (95% CI [51])**
Full Follow-up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	53 (0.401)	75 (0.554)	0.72 (0.50, 1.05)
Heart Failure Hospitalization + ED/OP	42 (0.317)	67 (0.493)	0.64 (0.43, 0.96)
Heart Failure Hospitalization	39 (0.298)	56 (0.417)	0.71 (0.47, 1.09)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	3 (0.025)	11 (0.089)	0.28 (0.08, 0.99)
Death	11 (0.086)	8 (0.061)	1.39 (0.56, 3.46)
Prior to COVID-19			COVID-19 Interaction p-value [52], p = 0.1579
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	43 (0.393)	70 (0.591)	0.67 (0.45, 0.99)
Heart Failure Hospitalization + ED/OP	33 (0.307)	62 (0.531)	0.58 (0.37, 0.89)
Heart Failure Hospitalization	30 (0.276)	51 (0.433)	0.64 (0.40, 1.01)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	3 (0.038)	11 (0.128)	0.30 (0.08, 1.06)
Death	10 (0.099)	8 (0.074)	1.34 (0.53, 3.39)

NYHA Class III

The baseline demographics and key characteristics for the NYHA Class III patients in the Treatment group and the Control group were balanced and listed in the table below.

Table 19. Demographics and Baseline Assessments – NYHA Class III Subjects

	Treatment (N = 322)	Control (N = 328)
Age - yr	68.8 ± 11.3 (322)	69.0 ± 11.2 (328)
Female Sex	39.8% (128/322)	38.7% (127/328)
Race		
▪ White	80.7% (260/322)	79.6% (261/328)
▪ Black	17.7% (57/322)	19.5% (64/328)
▪ Other	1.8% (6/322)	1.2% (4/328)

[48] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.

[49] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[50] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[51] Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.

[52] Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

Table 19. Demographics and Baseline Assessments – NYHA Class III Subjects

	Treatment (N = 322)	Control (N = 328)
Ethnicity		
▪ Hispanic	3.7% (12/322)	2.7% (9/328)
▪ Non-Hispanic	96.0% (309/322)	96.6% (317/328)
▪ Unknown	0.3% (1/322)	0.6% (2/328)
Body mass index - kg/m^2	33.9 ± 8.4 (322)	34.2 ± 8.5 (328)
Medical History		
▪ Ischemic etiology	40.7% (131/322)	35.1% (115/328)
▪ Diabetes	48.1% (155/322)	56.1% (184/328)
▪ Atrial flutter or fibrillation	61.8% (199/322)	57.9% (190/328)
Vital Signs and Hemodynamic Analyses		
▪ Left ventricular ejection fraction - %	39.9 ± 17.2 (322)	41.0 ± 17.3 (328)
▪ Left ventricular ejection fraction > 40%	47.2% (152/322)	50.6% (166/328)
▪ Pulmonary capillary wedge pressure - mmHg	17.2 ± 7.9 (321)	17.4 ± 7.6 (328)
▪ Cardiac output - L/min	4.96 ± 3.11 (322)	4.76 ± 1.59 (328)
▪ Cardiac index - L/min/m^2	2.29 ± 1.30 (322)	2.20 ± 0.67 (328)
Laboratory Analyses		
▪ Serum creatinine level - µmol/L	129.1 ± 44.2 (320)	134.5 ± 49.3 (326)
▪ Estimated glomerular filtration rate - ml/min/ 1.73m^2	53.7 ± 21.0 (320)	52.5 ± 21.6 (326)
▪ B-type natriuretic peptide level - pg/mL	550.8 ± 763.1 (181)	573.9 ± 1054.3 (176)
▪ N-terminal pro-B-type natriuretic peptide level - pg/mL	2258 ± 3316 (133)	2431 ± 3235 (140)
Treatment History		
▪ Previous cardiac resynchronization therapy	28.3% (91/322)	30.5% (100/328)
▪ Previous implantation of defibrillator	40.4% (130/322)	41.5% (136/328)
▪ Guideline-Directed Medical Therapy		
▪ ACE-Inhibitor or ARB or ARNi	62.1% (200/322)	61.9% (203/328)
▪ ARNi	27.3% (88/322)	26.5% (87/328)
▪ Beta Blocker	89.8% (289/322)	87.2% (286/328)
▪ Mineralocorticoid Receptor Antagonist	49.7% (160/322)	46.3% (152/328)
▪ Diuretic	97.2% (313/322)	95.7% (314/328)
▪ Hydralazine	17.4% (56/322)	14.0% (46/328)
▪ Nitrate	20.8% (67/322)	22.6% (74/328)
▪ SGLT2 Inhibitor	1.0% (1/98)	2.2% (2/92)
Enrollment Type		
▪ Heart failure hospitalization in year prior only	35.7% (115/322)	40.1% (131/327)
▪ Elevated natriuretic peptide level in 30 day prior only	44.4% (143/322)	40.4% (132/327)
▪ Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.9% (64/322)	19.6% (64/327)
Patient Reported Outcomes		
▪ KCCQ-12 at Baseline - Overall Summary Score	49.7 ± 23.1 (320)	50.7 ± 23.3 (325)
▪ 6MHW as Baseline - m	218.9 ± 116.1 (306)	218.1 ± 121.4 (312)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

The table below presents the primary endpoint event rates and components for NYHA Class III subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 114 primary endpoint events in the Treatment group compared with 141 events in the Control group. The difference represents a 20% reduction in the 12-month rate of primary endpoint events (0.552 events per patient in the Treatment group vs. 0.686 events per patient in the Control group, HR 0.80).

Table 20. Primary Endpoint and Components – NYHA Class III Subjects

Endpoint [53]	**Treatment (N = 322) Events (Rate** [54]**)**	**Control (N = 328) Events (Rate** [55]**)**	**Hazard Ratio (95% CI** [56]**)**
Full Follow-up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	171 (0.589)	198 (0.677)	0.87 (0.70, 1.08)
Heart Failure Hospitalization + ED/OP	147 (0.502)	171 (0.580)	0.86 (0.69, 1.09)
Heart Failure Hospitalization	127 (0.431)	156 (0.526)	0.82 (0.64, 1.04)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	20 (0.073)	15 (0.054)	1.34 (0.68, 2.62)
Death	24 (0.089)	27 (0.100)	0.90 (0.52, 1.55)
Prior to COVID-19			COVID-19 Interaction p-value [57], p = 0.2840
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	114 (0.552)	141 (0.686)	0.80 (0.62, 1.04)
Heart Failure Hospitalization + ED/OP	96 (0.460)	126 (0.606)	0.76 (0.58, 1.00)
Heart Failure Hospitalization	81 (0.389)	115 (0.555)	0.70 (0.52, 0.94)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	15 (0.077)	11 (0.057)	1.36 (0.62, 2.97)
Death	18 (0.108)	15 (0.091)	1.19 (0.60, 2.36)

NYHA Class IV

The table below presents the baseline demographics and key characteristics for the NYHA Class IV patients (N = 54).

Table 21. Demographics and Baseline Assessments – NYHA Class IV Subjects

	Treatment (N = 29)	**Control (N = 25)**
Age - yr	70.3 ± 8.8 (29)	67.3 ± 12.2 (25)
Female Sex	34.5% (10/29)	40.0% (10/25)
Race		
▪ White	69.0% (20/29)	84.0% (21/25)
▪ Black	27.6% (8/29)	12.0% (3/25)
▪ Other	3.4% (1/29)	4.0% (1/25)
Ethnicity		
▪ Hispanic	0.0% (0/29)	8.0% (2/25)
▪ Non-Hispanic	100.0% (29/29)	88.0% (22/25)
▪ Unknown	0.0% (0/29)	4.0% (1/25)
Body mass index - kg/m^2	33.4 ± 10.0 (29)	37.0 ± 11.2 (25)
Medical History		
▪ Ischemic etiology	44.8% (13/29)	28.0% (7/25)
▪ Diabetes	55.2% (16/29)	40.0% (10/25)
▪ Atrial flutter or fibrillation	62.1% (18/29)	56.0% (14/25)
Vital Signs and Hemodynamic Analyses		
▪ Left ventricular ejection fraction - %	34.1 ± 17.8 (29)	42.2 ± 16.7 (25)
▪ Left ventricular ejection fraction > 40%	34.5% (10/29)	52.0% (13/25)

[53] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.

[54] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[55] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[56] Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.

[57] Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

Table 21. Demographics and Baseline Assessments – NYHA Class IV Subjects

	Treatment (N = 29)	Control (N = 25)
▪ Pulmonary capillary wedge pressure - mmHg	19.6 ± 9.1 (29)	18.5 ± 8.5 (25)
▪ Cardiac output - L/min	4.40 ± 1.16 (29)	4.98 ± 1.61 (25)
▪ Cardiac index - L/min/m^2	2.08 ± 0.53 (29)	2.23 ± 0.74 (25)
Laboratory Analyses		
▪ Serum creatinine level - µmol/L	148.9 ± 58.7 (29)	149.9 ± 56.2 (25)
▪ Estimated glomerular filtration rate - ml/min/1.73m^2	49.3 ± 23.0 (29)	45.3 ± 17.2 (25)
▪ B-type natriuretic peptide level - pg/mL	386.8 ± 482.7 (19)	378.9 ± 329.9 (11)
▪ N-terminal pro-B-type natriuretic peptide level - pg/mL	4653 ± 6525 (10)	3092 ± 3946 (13)
Treatment History		
▪ Previous cardiac resynchronization therapy	41.4% (12/29)	40.0% (10/25)
▪ Previous implantation of defibrillator	37.9% (11/29)	36.0% (9/25)
▪ Guideline-Directed Medical Therapy		
▪ ACE-Inhibitor or ARB or ARNi	62.1% (18/29)	48.0% (12/25)
▪ ARNi	31.0% (9/29)	28.0% (7/25)
▪ Beta Blocker	82.8% (24/29)	76.0% (19/25)
▪ Mineralocorticoid Receptor Antagonist	48.3% (14/29)	56.0% (14/25)
▪ Diuretic	100.0% (29/29)	96.0% (24/25)
▪ Hydralazine	27.6% (8/29)	16.0% (4/25)
▪ Nitrate	20.7% (6/29)	16.0% (4/25)
▪ SGLT2 Inhibitor	0.0% (0/8)	0.0% (0/7)
Enrollment Type		
▪ Heart failure hospitalization in year prior only	27.6% (8/29)	44.0% (11/25)
▪ Elevated natriuretic peptide level in 30 day prior only	44.8% (13/29)	24.0% (6/25)
▪ Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	27.6% (8/29)	32.0% (8/25)
Patient Reported Outcomes		
KCCQ-12 at Baseline - Overall Summary Score	39.0 ± 20.2 (29)	40.5 ± 22.5 (25)
6MHW as Baseline - m	153.2 ± 119.3 (26)	164.4 ± 108.2 (24)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

The table below presents the primary endpoint event rates and components for NYHA Class IV subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 20 primary endpoint events in the Treatment group compared with 13 events in the Control group. The hazard ratio was 1.91 with a wide confidence interval.

Table 22. Primary Endpoint and Components – NYHA Class IV Subjects

Endpoint [58]	Treatment (N = 29) Events (Rate [59])	Control (N = 25) Events (Rate [60])	Hazard Ratio (95% CI [61])
Full Follow-up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	29 (1.527)	16 (0.910)	1.68 (0.88, 3.20)
Heart Failure Hospitalization + ED/OP	24 (1.337)	14 (0.840)	1.59 (0.80, 3.18)
Heart Failure Hospitalization	19 (1.130)	13 (0.826)	1.37 (0.66, 2.84)

[58] Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.

[59] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[60] Event Rate is an annualized rate estimated from the Anderson-Gill model.

[61] Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.

Table 22. Primary Endpoint and Components – NYHA Class IV Subjects

Endpoint	Treatment (N = 29) Events (Rate)	Control (N = 25) Events (Rate)	Hazard Ratio (95% CI)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	5 (0.535)	1 (0.121)	4.43 (0.52, 38.0)
Death	5 (0.279)	2 (0.123)	2.26 (0.44, 11.6)
Prior to COVID-19			COVID-19 Interaction p-value [62], p = 0.9455
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	20 (3.123)	13 (1.632)	1.91 (0.88, 4.18)
Heart Failure Hospitalization + ED/OP	18 (3.110)	11 (1.516)	2.05 (0.88, 4.77)
Heart Failure Hospitalization	13 (2.597)	10 (1.493)	1.74 (0.68, 4.43)
HF Emergency Department/ Hospital Outpatient Visit (ED/OP)	5 (0.576)	1 (0.128)	4.51 (0.52, 38.9)
Death	2 (0.268)	2 (0.223)	1.20 (0.18, 8.15)

Summary/Key Takeaways

Despite the limitations of COVID-19 occurring during the follow-up of the study, the results of the GUIDE-HF Randomized Arm support the continued safety and effectiveness of the CardioMEMS HF System within an expanded population, as shown by reduced HF hospitalizations. The treatment benefit observed in NYHA Class II subjects and those with elevated NT-proBNP/BNP but without a recent hospitalization for HF suggests that intervention in NYHA Class II heart failure, even prior to the occurrence of HF events, can provide benefit.

Pivotal Data from the CHAMPION Trial

CHAMPION (CardioMEMS HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients) was a prospective, multicenter, single-blind, randomized, clinical trial in 550 patients across 64 centers in the United States.

Purpose

The goal of CHAMPION was to determine if physicians could reduce HF hospitalizations by managing patient PA pressures using the CardioMEMS HF System.

Methods

Study Design

550 patients with NYHA Class III HF and a prior HF hospitalization within 12 months were randomized to standard of care plus the CardioMEMS HF System (Treatment group; 270 patients) or to standard of care only (Control group; 280 patients). All patients were implanted with the PA sensor and took daily readings from home. Patients were enrolled regardless of their baseline ejection fraction so that patients with both reduced and preserved systolic function were included. Physicians had access to PA pressure information for patients in the Treatment group but not for patients in the Control group.

Following the completion of Randomized Access, patients transitioned to a period of Open Access, during which PA pressures were provided to physicians for patients in both the Treatment and the Control groups. Specifically, physicians continued to have access to the Treatment group's PA pressures in an unchanged manner, whereas access to the Control group's PA pressure was provided for the first time.

Follow-Up Schedule

After RHC and sensor implantation, all patients had follow-up study visits at 1 month, 3 months, 6 months, and every 6 months thereafter until study termination.

Study Endpoints

The primary and secondary endpoints were evaluated after 6 months of patient follow-up. The primary safety endpoints were (1) Freedom from device / system-related complications (DSRC), and (2) Freedom from pressure sensor failures. The primary efficacy endpoint was the rate of HF hospitalizations. All hospitalizations were adjudicated by an independent Clinical Events Committee (CEC) who were blinded to treatment assignment. Secondary endpoints were tested in a hierarchical fashion and included changes in PA pressures, proportion of subjects hospitalized for HF, days alive outside of the hospital for HF, and quality of life. Because blinded follow-up continued until the last patient completed 6 months of follow-up, the average patient follow-up was much longer (17.6 months) and pre-specified supplementary analyses were conducted on the full duration of follow-up data (Randomized Access).

Patient Demographics and Disposition

575 patients were consented for trial enrollment and underwent right heart catheterization (RHC). Of these 575 patients, 25 (4.3%) underwent a RHC but did not receive an implant primarily because of anatomical/physiological conditions identified during the RHC. Of the 550 randomized patients, 270 were assigned to the Treatment group and 280 to the Control group. The two groups were similar with respect to baseline characteristics (see table below).

[62] Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

Table 23. Patient Demographics

	Randomized Group		
Variables	**Treatment (N=270)**	**Control (N=280)**	**p-value [63]**
Age (years)	61.3 ± 12.98 (270)	61.8 ± 12.73 (280)	0.5927
Male	194/270 (71.9%)	205/280 (73.2%)	0.7745
Race (White)	196/270 (72.6%)	205/280 (73.2%)	0.9236
Systolic BP (mmHg)	121.2 ± 22.52 (270)	123.2 ± 21.01 (280)	0.1286
Heart Rate (bpm)	72.4 ± 12.91 (269)	73.0 ± 12.14 (280)	0.4873
BMI	30.5 ± 6.50 (270)	30.9 ± 7.35 (280)	0.6228
BUN (mg/dL)	29.6 ± 17.99 (248)	28.1 ± 16.17 (267)	0.6325
Creatinine (mg/dL)	1.4 ± 0.47 (270)	1.4 ± 0.42 (280)	0.5560
GFR (mL/min/1.73m^2)	60.4 ± 22.50 (270)	61.8 ± 23.20 (280)	0.5638
Ejection Fraction (EF>=40%)	62/270 (23.0%)	57/279 (20.4%)	0.5343
Cardiac Output (L/min)	4.5 ± 1.41 (270)	4.6 ± 1.54 (278)	0.5499
Cardiac Index (L/min/m^2)	2.1 ± 0.59 (270)	2.2 ± 0.64 (278)	0.4405
PVR	2.9 ± 2.02 (270)	2.7 ± 1.82 (278)	0.4609
PA Wedge Pressure (mmHg)	17.5 ± 7.97 (270)	19.0 ± 8.12 (280)	0.0276
PA Mean Pressure (mmHg)	28.9 ± 9.92 (270)	29.9 ± 10.05 (280)	0.3021
CRT-D/ICD Implant	179/270 (66.3%)	197/280 (70.4%)	0.3145
Ischemic Cardiomyopathy	158/270 (58.5%)	174/280 (62.1%)	0.4327
Hypertension	207/270 (76.7%)	220/280 (78.6%)	0.6100
Hyperlipidemia	204/270 (75.6%)	218/280 (77.9%)	0.5458
Coronary Artery Disease	182/270 (67.4%)	202/280 (72.1%)	0.2290
History of MI	134/270 (49.6%)	137/280 (48.9%)	0.9320
Diabetes Mellitus	130/270 (48.1%)	139/280 (49.6%)	0.7337
AFIB	120/270 (44.4%)	135/280 (48.2%)	0.3932
COPD	76/270 (28.1%)	83/280 (29.6%)	0.7078
ACE/ARB use	205/270 (75.9%)	222/280 (79.3%)	0.3584
Beta Blocker use	243/270 (90.0%)	256/280 (91.4%)	0.6595

The mean follow-up during Randomized Access was 17.6 months for a total duration of approximately 800 patient years. During the course of Randomized Access, 93 patients in the Treatment group and 110 patients in the Control group exited the study with the primary reason being death.

A total of 347 patients (177 in the Treatment group and 170 in the Control group) completed Randomized Access and entered Open Access. The mean follow-up during Open Access was 13 months for a total duration of approximately 400 patient years. During the course of Open Access, 58 patients in the Treatment group and 43 patients in the Control group exited the study with the primary reason being death.

Primary and Secondary Endpoint Results

Primary Safety Endpoints

CHAMPION met the two primary safety endpoints: (1) Freedom from device/system related complications (DSRC) and (2) Freedom from sensor failure. The protocol pre-specified objective performance criteria (OPC) were that at least 80% of patients were to be free from DSRC and at least 90% were to be free from pressure sensor failure. Of the 575 patients in the safety population, 567 (98.6%) were free from DSRC at 6 months (lower confidence limit 97.3%, p<0.0001). This lower limit of 97.3% is greater than the pre-specified OPC of 80% (see tables below). There were no sensor explants or repeat implants and all sensors were operational at 6 months for a freedom from sensor failure of 100% (lower confidence limit 99.3%, p<0.0001). This lower limit of 99.3% is greater than the pre-specified OPC of 90% (see Primary Safety Endpoint – Freedom from Pressure Sensor Failures table).

Table 24. Primary Safety Endpoint – Freedom from Device/System Related Complications

Device/System Related Complications (n=575)		**Lower 95.2% [64] Confidence Limit**	**Objective Performance Criterion (OPC)**	**p-value [65]**
Yes	**No**			
8 (1.4%) [66]	567 (98.6%)	97.3%	80%	p<0.0001

[63] Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.
[64] Exact 95.2% Clopper-Pearson lower confidence limit
[65] p-value from exact test of binomial proportions compared to 80% for all patients
[66] DSRCs (8 total) by group: Consented but not randomized (2), Treatment (3), Control (3)

Table 25. Primary Safety Endpoint – Description of Device/System Related Complications

Description	Number of Subjects with Device or System related complication (%) (N = 575)
Hemoptysis	1 (0.2%)
Sensor did not deploy	1 (0.2%)
Transient Ischemic Attack (TIA)	1 (0.2%)
Atypical chest pain	1 (0.2%)
Sepsis → death	1 (0.2%)
Atrial arrhythmia → death	1 (0.2%)
Arterial embolism (upper extremity)	1 (0.2%)
Pulmonary artery (in-situ) thrombus	1 (0.2%)
Total Subjects Experiencing a DSRC	**8 (1.4% [67], 95.2% LCB 97.3%)**

Table 26. Primary Safety Endpoint – Freedom from Pressure Sensor Failures

Pressure Sensor Failures (n=550)		Lower 95.2% Confidence Limit [68]	Objective Performance Criterion (OPC)	p-value [69]
Yes	**No**			
0 (0.0%)	550 (100%)1	99.3%	90%	p<0.0001

Primary Efficacy Endpoint

The primary efficacy endpoint of the CHAMPION trial was the rate of HF hospitalizations during the first 6 months of Randomized Access. There were 84 HF hospitalizations in the Treatment group compared with 120 HF hospitalizations in the Control group. This difference between the groups represented a 28% reduction in the 6-month rate of HF hospitalization in the Treatment group (0.32 hospitalizations per patient in the Treatment group vs. 0.44 hospitalizations per patient in the Control group, HR 0.72, 95% CI 0.60-0.85, p = 0.0002) (Primary Efficacy Endpoint – HF Hospitalization rates During First 6 months of Randomized Access table).

Table 27. Primary Efficacy Endpoint – HF Hospitalization rates During First 6 months of Randomized Access

	Number of HF Hospitalizations	6 Month HF Hospitalization Rate	Hazard Ratio (95% CI) [p-value] [70]
Treatment Group (n=270)	84	0.32	0.72 (0.60-0.85) p=0.0002
Control Group (n=280)	120	0.44	

Secondary Endpoints

The four secondary efficacy endpoints were analyzed hierarchically at 6 months (table below). At baseline, both Treatment and Control patients had similar PA mean pressures. When compared with patients in the Control group, the patients in the Treatment group had greater reduction in mean PA pressure (p=0.0077); were less likely to be hospitalized for heart failure (p=0.0292); spent more days alive outside of the hospital for heart failure (p=0.0280); and reported a better quality of life (Minnesota Living with Heart Failure Questionnaire) (p=0.0236).

Table 28. Secondary Efficacy Endpoints at 6 Months

	Treatment	Control	p-value
Change from baseline in mean pulmonary artery pressure, area under the curve (mean mmHg-days)	-155.7 (n=265)	33.1 (n=272)	0.0077 [71]
Proportion of patients hospitalized for heart failure (%)	55 (20.4%) (n=270)	80 (28.6%) (n=280)	0.0292 [72]
Days alive outside the hospital for heart failure (mean)	174.4 (n=270)	172.1 (n=280)	0.0280 [73]
Minnesota Living with Heart Failure Questionnaire (mean[median])	45.2 [45.0] (n=229)	50.6 [52.0] (n=236)	0.0236 [74]

Medical Management

Physicians responded to Treatment patients' elevated PA pressures by making medication changes to lower PA pressures in an attempt to reduce the risk for HF hospitalization. Physicians documented all medication changes for all patients and indicated whether the change was made in response to PA pressures or standard of care information. During the 6-month follow-up period, physicians made 1113 HF medication

[67] Pressure sensor failure counts by group: Treatment (0), Control (0)
[68] Exact 95.2% Clopper-Pearson lower confidence limit
[69] p-value from exact test of binomial proportions compared to 90% for all patients
[70] p-value and hazard ratio from negative binomial regression model
[71] p-value from analysis of covariance with baseline pressure as the covariate
[72] p-value from Fisher's exact test
[73] p-value from Wilcoxon rank sum test after controlling for subject duration in study (i.e., days alive outside the hospital / subject duration x 180)
[74] p-value from two-group t-test

changes in the Treatment group and 1061 HF medication changes in the Control group in response to standard of care information. In the Treatment group only, physicians made 1404 HF medication changes in response to PA pressures, primarily through diuretics and vasodilators. This incremental HF management in response to PA pressures using the CardioMEMS HF System led to a significant reduction in HF hospitalizations.

Results from the Entire Randomized Access Period

HF Hospitalizations

During the entire Randomized Access period, the rate of HF hospitalizations was 33% lower in the Treatment group than in the Control group (0.46 vs. 0.68 annualized HF hospitalization rates, HR 0.67, 95%CI 0.55-0.80) (table below). The magnitude of the effect during the entire Randomized Access period was slightly larger than that seen during the 6-month primary endpoint period (33% vs. 28%), indicating durability of the treatment effect. The number needed to treat (NNT) per year to prevent one HF hospitalization was 4. For every 100 patients treated, 23 HF hospitalizations would be prevented per year.

Table 29. HF Hospitalization Rates During Randomized Access

	Number of HF Hospitalizations	Annualized HF Hospitalization Rate	Hazard Ratio [75] (95% CI)	NNT Per Year to Prevent One HF Hospitalization
Treatment Group (n=270)	182	0.46	0.67 (0.55-0.80)	4
Control Group (n=280)	279	0.68		

Mortality

The proportion of patients who died in the Treatment group (18.5%) was smaller than in the Control Group (22.9%) with a relative risk reduction of 20% (HR 0.80, 95% CI 0.55 – 1.15).

Freedom from Death or First HF Hospitalization

The proportion of patients who died or had at least one HF hospitalization in the Treatment group (44.8%) was smaller than in the Control Group (51.8%) with a relative risk reduction of 23% (HR 0.77, 95% CI 0.60 – 0.98).

All Cause Hospitalizations

All cause hospitalizations were reduced in the Treatment group (554 in the Treatment group vs. 672 in the Control group, HR 0.84, 95% CI 0.75 – 0.95). The NNT per year to prevent one all cause hospitalization was 4. For every 100 patients treated, 26 all cause hospitalizations would be prevented per year.

Death or All Cause Hospitalizations

Death or all cause hospitalizations were reduced in the Treatment group (604 in the Treatment group vs. 736 in the Control group, HR 0.84, 95% CI 0.76 – 0.94). The NNT per year to prevent one death or all cause hospitalization was 4. For every 100 patients treated, 29 deaths or all cause hospitalizations would be prevented per year.

Results from the Open Access Period (Longitudinal Analysis)

In the Open Access period, physicians were given access to PA pressures in the Control group for the first time while access to PA pressures for the Treatment group continued. In the Control group, new physician access to PA pressures resulted in a 48% reduction in HF hospitalization rates (0.36 vs. 0.68, HR 0.52, 95% CI 0.40-0.69, p<0.0001*). In the Treatment group, continued physician access to PA pressures resulted in the maintenance of low HF hospitalization rates (0.45 vs. 0.48, HR 0.93, 95% CI 0.70-1.22, p=0.5838*).

To account for potential longitudinal confounders, the change in HF hospitalization rates in the Control group as result of new access to PA pressures was compared to the change in HF hospitalization rates in the Treatment group. The change in HF hospitalization rates in the Control group was significantly greater than in the Treatment group (HR 0.56, 95% CI 0.38-0.83, p=0.0040*), indicating that the significant 48% reduction in HF hospitalization rates observed in the Control group was the result of physician access to PA pressure and not longitudinal effects.

(*P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Treatment Effects in Women

The CHAMPION study was not powered to show statistical significance for gender, thus a complete determination of the effect of the device in women cannot be made. At the request of FDA, a post-hoc gender analysis was conducted for the CHAMPION study, and the initial finding of a treatment-by-gender interaction for the effect of the CardioMEMS device on the HF hospitalization rate was related to (1) fewer women being in the study and the short duration of follow-up leading to a small number of events in women; and (2) the low HF hospitalization rate in Control women due to an early excess of deaths in women in the Control group, which acted as a competing risk to censor the occurrence of hospitalizations for heart failure.

A further analysis of the treatment-by- gender interaction was performed over the full period of Randomized Access and by incorporating death in the Cox Proportional Hazards. When these limitations and confounding issues were evaluated over the full period, there was neither a qualitative nor quantitative treatment-by-gender interaction and the treatment effect remained positive, independent of gender. However, the analyses conducted do not alleviate the possibility of a diminished treatment effect in women. Given the small number of women enrolled and small number of events observed in women, the true treatment effect in this group remains uncertain. In order to further complement and evaluate the results obtained during the CHAMPION study, the effect of the device in women was studied as part of the post approval study. Please refer to the results in the Long-term Data section (page 80).

The figures below depict the Freedom from HF Hospitalization and Freedom from Death for Men and Women over the Full Randomized Period (Part 1). The last figure below depicts the composite endpoint of Freedom from HF Hospitalization or Death for Men and Women over the Full Randomized Period (Part 1). They illustrate the apparent difference in treatment effect by gender. As seen in the first figure below, for HF hospitalizations alone, treatment and control women have similar outcomes. However, as seen in the second figure below, control women had an increased early mortality creating a competing risk for HF hospitalizations i.e., fewer control women were alive to have HF hospitalizations. The last figure below examines Freedom from HF Hospitalization or Death and indicates a non-significant trend favoring women in the treatment group.

[75] Hazard ratio from Andersen-Gill model

Figure 84. Freedom from HF Hospitalization over the Full Randomized Period (Part 1).

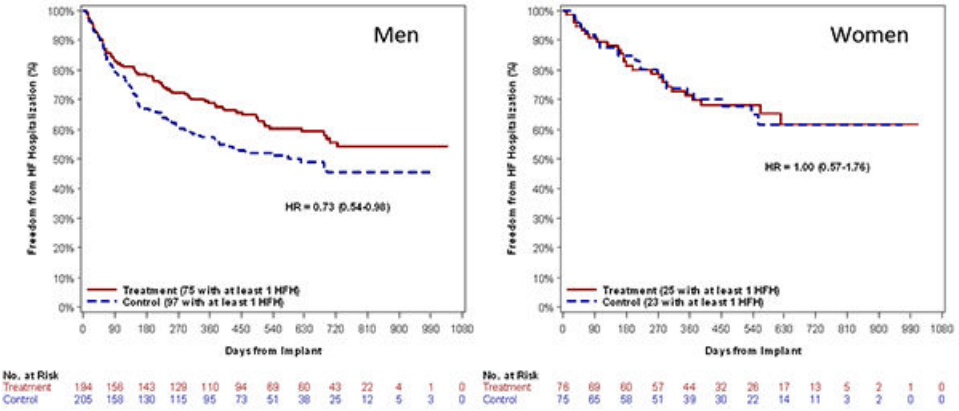


Figure 85. Freedom from Death over the Full Randomized Period (Part 1).

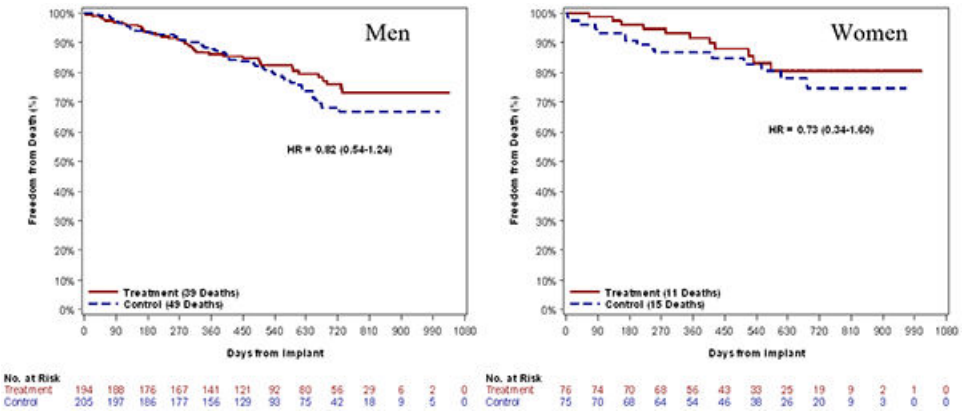
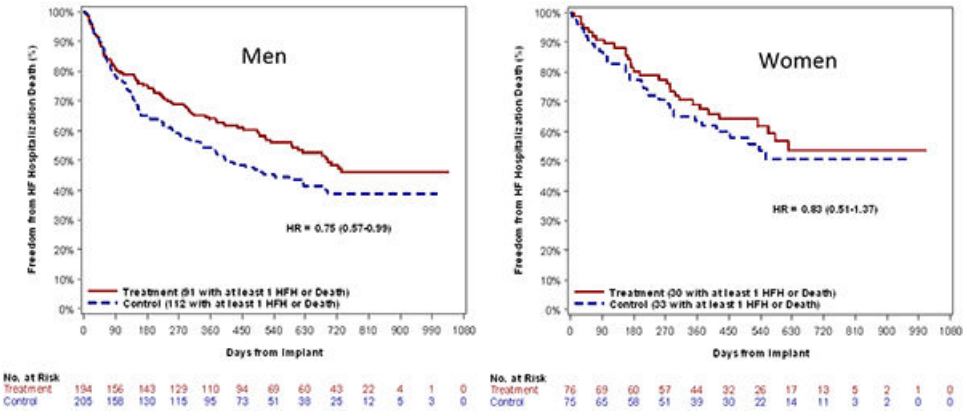


Figure 86. Freedom from HF Hospitalization or Death over the Full Randomized Period (Part 1).



Also performed were an Anderson-Gill Model with Frailty, Anderson Gill Model with Robust Sandwich Estimates (RSE) and Negative Binomial Regression using an endpoint of time to HF hospitalization or death in Part 1 and Part 1 + Part 2. As seen in the gray rows in the tables below, all the competing risk analyses taking death into account as a competing risk show that there was no evidence of a treatment-by-gender interaction if a p-value of 0.05 is used. However, when analyses for interaction by gender are conducted, a p-value of 0.15 is typically used because the analysis is typically not powered appropriately. When considering a p-value of 0.15, there was some evidence of treatment-by-gender interaction in the competing risk analyses under the following models:

- AG Model with Frailty for Part 1
- NB Regression for Part 1
- AG Model with Robust Sandwich Estimate for Part 1 + Part 2
- GEE NB Regression for Part 1 + Part 2

Table 30. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Part 1			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.113	0.289	0.6968

Table 30. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Cox Model: Endpoint of first HFR hospitalization	-0.330	0.327	0.3131
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.373	0.239	0.1211
AG Model with Frailty: Endpoint of HFR hospitalization	-0.531	0.262	0.0459
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.433	0.316	0.1712
AG Model with RSE: Endpoint of HFR hospitalization	-0.577	0.360	0.1094
NB Regression: Endpoint of HFR hospitalization or Death	-0.412	0.242	0.0896
NB Regression: Endpoint of HFR hospitalization	-0.573	0.191	0.0027
Part 1 + Part 2			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.204	0.249	0.4121*
Cox Model: Endpoint of first HFR hospitalization	-0.427	0.284	0.1331*
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.376	0.274	0.1697*
AG Model with Frailty: Endpoint of HFR hospitalization	-0.588	0.271	0.0301*
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.477	0.274	0.0816*
AG Model with RSE: Endpoint of HFR hospitalization	-0.642	0.313	0.0399*
GEE NB Regression: Endpoint of HFR hospitalization or Death	-0.488	0.283	0.0841*
GEE NB Regression: Endpoint of HFR hospitalization	-0.761	0.319	0.0172*

Table 31. The Treatment vs. Control effects by Gender over Part 1 and over Part 1+ Part 2 under different models

Males	Hazard Ratio	p-value
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.67	0.0007
AG Model with Frailty: Endpoint of HFR hospitalization	0.64	0.0004
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.70	0.0176*
AG Model with Frailty: Endpoint of HFR hospitalization	0.53	<0.0001*
Females	Hazard Ratio	p-value
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.99	0.9440
AG Model with Frailty: Endpoint of HFR hospitalization	1.07	0.7584
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.80	0.4512*
AG Model with Frailty: Endpoint of HFR hospitalization	0.61	0.1482*

(*P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Non-Serious Adverse Device Events

There were 17 non-serious adverse device events that occurred over Part 1. There were no additional non-serious adverse device events over Part 2 of the clinical trial. These events were rare and are well known adverse events that occur during right heart catheterization procedures (table below).

Table 32. Non-serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	5 (1.9%)	6	7 (2.5%)	11	12 (2.2%)	17	0 (0%)	0
General disorders and administration site conditions	1 (0.4%)	1 (16.7%)	4 (1.4%)	6 (54.5%)	5 (0.9%)	7 (41.2%)	0 (0%)	0 (0%)
Catheter site bleeding	0	0	1	1	1	1	0	0
Catheter site ecchymosis	0	0	1	1	1	1	0	0
Catheter site hematoma	0	0	1	1	1	1	0	0
Chest discomfort	0	0	1	1	1	1	0	0

Table 32. Non-serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Chest pain	0	0	1	1	1	1	0	0
Non-cardiac chest pain	1	1	0	0	1	1	0	0
Vessel puncture site pain	0	0	1	1	1	1	0	0
Investigations	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)	0 (0%)	0 (0%)
Cardiac monitoring abnormal	1	1	0	0	1	1	0	0
Heart rate irregular	0	0	1	1	1	1	0	0
Serum creatinine increased	1	1	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)	0 (0%)	0 (0%)
Hemoptysis	1	1	1	1	2	2	0	0
Dyspnea	1	1	0	0	1	1	0	0
Cardiac disorders	1 (0.4%)	1 (16.7%)	1 (0.4%)	1 (9.1%)	2 (0.4%)	2 (11.8%)	0 (0%)	0 (0%)
Congestive heart failure	1	1	0	0	1	1	0	0
Ventricular tachycardia	0	0	1	1	1	1	0	0
Nervous system disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Dizziness	0	0	1	1	1	1	0	0
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Vessel perforation	0	0	1	1	1	1	0	0

Non-Serious Adverse Events not related to the device

Table 33. Non-Serious Adverse Events not related to the device Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	216 (80.0%)	1229	223 (79.6%)	1135	439 (79.8%)	2364	219 (63.1%)	787
Blood and lymphatic system disorders	27 (10.0%)	37	22 (7.9%)	28	49 (8.9%)	65	13 (3.7%)	16
Cardiac disorders	81 (30.0%)	140	69 (24.6%)	117	150 (27.3%)	257	49 (14.1%)	71
Congenital, familial and genetic disorders	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.9%)	3
Ear and labyrinth disorders	6 (2.2%)	6	2 (0.7%)	2	8 (1.5%)	8	2 (0.6%)	2
Endocrine disorders	4 (1.5%)	4	9 (3.2%)	10	13 (2.4%)	14	7 (2.0%)	7
Eye disorders	12 (4.4%)	12	14 (5.0%)	16	26 (4.7%)	28	7 (2.0%)	8
Gastrointestinal disorders	64 (23.7%)	104	60 (21.4%)	96	124 (22.5%)	200	48 (13.8%)	70
General disorders and administration site conditions	64 (23.7%)	102	45 (16.1%)	80	109 (19.8%)	182	50 (14.4%)	62
Hepatobiliary disorders	1 (0.4%)	1	7 (2.5%)	10	8 (1.5%)	11	3 (0.9%)	3
Immune system disorders	4 (1.5%)	4	4 (1.4%)	4	8 (1.5%)	8	4 (1.2%)	4
Infections and infestations	76 (28.1%)	129	91 (32.5%)	150	167 (30.4%)	279	65 (18.7%)	99
Injury, poisoning and procedural complications	32 (11.9%)	44	32 (11.4%)	37	64 (11.6%)	81	32 (9.2%)	43
Investigations	32 (11.9%)	51	26 (9.3%)	40	58 (10.5%)	91	22 (6.3%)	25
Metabolism and nutrition disorders	66 (24.4%)	116	52 (18.6%)	88	118 (21.5%)	204	37 (10.7%)	53
Musculoskeletal and connective tissue disorders	49 (18.1%)	75	58 (20.7%)	73	107 (19.5%)	148	56 (16.1%)	70
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2%)	8	9 (3.2%)	9	15 (2.7%)	17	6 (1.7%)	7
Nervous system disorders	61 (22.6%)	86	50 (17.9%)	67	111 (20.2%)	153	47 (13.5%)	56
Psychiatric disorders	34 (12.6%)	46	29 (10.4%)	36	63 (11.5%)	82	25 (7.2%)	31
Renal and urinary disorders	33 (12.2%)	55	35 (12.5%)	45	68 (12.4%)	100	21 (6.1%)	21
Reproductive system and breast disorders	7 (2.6%)	8	16 (5.7%)	16	23 (4.2%)	24	11 (3.2%)	13

Table 33. Non-Serious Adverse Events not related to the device Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Respiratory, thoracic and mediastinal disorders	68 (25.2%)	97	70 (25.0%)	117	138 (25.1%)	214	47 (13.5%)	66
Skin and subcutaneous tissue disorders	23 (8.5%)	26	24 (8.6%)	28	47 (8.5%)	54	9 (2.6%)	9
Surgical and medical procedures	17 (6.3%)	21	16 (5.7%)	20	33 (6.0%)	41	16 (4.6%)	19
Vascular disorders	41 (15.2%)	57	39 (13.9%)	46	80 (14.5%)	103	27 (7.8%)	29

Serious Adverse Events Over Part 1 and Part 2

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	198 (73.3%)	797	217 (77.5%)	956	415 (75.5%)	1753	201 (57.9%)	647
Cardiac disorders	138 (51.1%)	333	151 (53.9%)	443	289 (52.5%)	776	119 (34.3%)	238
Congestive heart failure	99	204	121	274	220	478	80	140
Heart failure	10	15	13	22	23	37	10	12
Ventricular tachycardia	10	14	12	16	22	30	8	9
Myocardial infarction	7	7	14	14	21	21	9	9
Cardiac pain	13	19	7	22	20	41	0	0
Atrial fibrillation	3	5	10	11	13	16	4	4
Cardiomyopathy	5	6	8	11	13	17	6	7
Cardiopulmonary arrest	3	3	7	7	10	10	3	3
Unstable angina	4	4	5	5	9	9	4	6
Coronary artery disease	5	5	3	3	8	8	4	4
Ventricular arrhythmia	3	3	5	7	8	10	0	0
Ventricular fibrillation	5	6	2	2	7	8	2	2
Anginal discomfort	1	1	5	8	6	9	2	4
Cardiac arrest	2	2	4	4	6	6	6	6
Ischemic cardiomyopathy	3	4	3	3	6	7	6	7
Atrial flutter	2	2	3	3	5	5	3	3
Cardiogenic shock	2	2	3	3	5	5	3	3
Acute decompensated heart failure	2	2	1	1	3	3	0	0
ADHF	2	2	0	0	2	2	0	0
Acute coronary syndrome	1	2	1	1	2	3	1	1
Arrhythmia	1	1	1	1	2	2	1	1
Atrial arrhythmia	1	1	1	1	2	2	0	0
Cardiac failure	0	0	2	2	2	2	0	0
Heart disease, unspecified	1	1	1	1	2	2	1	1
Non-ischemic cardiomyopathy	1	1	1	1	2	2	0	0
Sick sinus syndrome	1	1	1	1	2	2	0	0
Angina unstable	0	0	1	1	1	1	0	0
Arrhythmia ventricular	1	1	0	0	1	1	0	0
Arrhythmia ventricular (NOS)	1	1	0	0	1	1	0	0
Atrial tachycardia	0	0	1	1	1	1	0	0
Bradycardia	0	0	1	1	1	1	2	2
Bradycardia-tachycardia syndrome	0	0	1	1	1	1	0	0
Cardiac arrhythmia	1	1	0	0	1	1	1	1

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Cardiomegaly	0	0	1	1	1	1	0	0
Cardiorenal syndrome	1	1	0	0	1	1	1	2
Chronic heart failure	1	1	0	0	1	1	0	0
Congestive cardiac failure aggravated	0	0	1	1	1	1	0	0
Coronary artery disease progression	1	1	0	0	1	1	0	0
Coronary atherosclerosis	1	1	0	0	1	1	0	0
Coronary spasm	0	0	1	1	1	1	0	0
Decompensated heart failure	1	1	0	0	1	1	0	0
End stage cardiac failure	0	0	1	1	1	1	0	0
Heart failure, congestive	0	0	1	1	1	1	0	0
Heart valve incompetence	1	1	0	0	1	1	0	0
Intermediate coronary syndrome	0	0	1	1	1	1	0	0
Junctional tachycardia	0	0	1	1	1	1	0	0
Left ventricular dysfunction	1	1	0	0	1	1	0	0
Mitral valve incompetence	1	1	0	0	1	1	1	1
Multi-valvular regurgitation	0	0	1	1	1	1	0	0
Non ST segment elevation myocardial infarction	1	1	0	0	1	1	0	0
Non-sustained ventricular tachycardia	1	1	0	0	1	1	0	0
Pacemaker mediated tachycardia	1	1	0	0	1	1	0	0
Paroxysmal supraventricular tachycardia	1	1	0	0	1	1	0	0
Pericardial disease	1	1	0	0	1	1	0	0
Pericardial effusion	1	1	0	0	1	1	0	0
Pericarditis	0	0	1	1	1	1	1	1
Premature ventricular contractions	0	0	1	1	1	1	0	0
Supraventricular tachycardia	0	0	1	1	1	1	0	0
Sustained ventricular tachycardia	1	1	0	0	1	1	0	0
Tachycardia	0	0	1	1	1	1	0	0
Tricuspid insufficiency	0	0	1	1	1	1	0	0
Ventricular ectopic beats	1	1	0	0	1	1	0	0
Ventricular rhythm	0	0	1	1	1	1	0	0
Wide complex tachycardia	0	0	1	1	1	1	0	0
Wide complex ventricular tachycardia	1	1	0	0	1	1	0	0
Asystole	0	0	0	0	0	0	2	2
Congestive cardiomyopathy	0	0	0	0	0	0	1	1
End stage heart disease	0	0	0	0	0	0	1	1
Hemopericardium	0	0	0	0	0	0	1	1
Palpitation	0	0	0	0	0	0	1	1
Paroxysmal atrial fibrillation	0	0	0	0	0	0	1	1
Polymorphic ventricular tachycardia	0	0	0	0	0	0	1	1
Tachycardia supraventricular	0	0	0	0	0	0	1	1
Infections and infestations	45 (16.7%)	62	61 (21.8%)	90	106 (19.3%)	152	52 (15.0%)	76
Pneumonia	11	11	15	16	26	27	17	19
Urinary tract infection	5	7	5	6	10	13	5	5

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Bronchitis	3	3	5	6	8	9	3	3
Cellulitis	1	1	6	7	7	8	1	1
Sepsis	3	4	4	4	7	8	7	9
Acute bronchitis	1	1	4	4	5	5	2	2
Bacteremia	1	1	3	5	4	6	2	2
Upper respiratory infection	2	2	2	2	4	4	1	1
Influenza	3	3	0	0	3	3	0	0
Cellulitis of leg	0	0	2	2	2	2	0	0
Cellulitis of legs	0	0	2	2	2	2	0	0
Central line infection	0	0	2	2	2	2	2	2
Endocarditis	0	0	2	2	2	2	0	0
Foot infection	2	3	0	0	2	3	0	0
Gastroenteritis	2	3	0	0	2	3	3	3
Incision site infection	1	3	1	4	2	7	1	1
Infection	0	0	2	2	2	2	1	1
Osteomyelitis	1	1	1	1	2	2	1	1
Pyelonephritis	1	1	1	1	2	2	0	0
Respiratory infection	1	1	1	1	2	2	0	0
Viral gastroenteritis	1	1	1	1	2	2	0	0
Abscess	1	1	0	0	1	1	0	0
Acute diverticulitis	1	1	0	0	1	1	0	0
Acute pyelonephritis	0	0	1	1	1	1	0	0
Bacterial endocarditis	0	0	1	1	1	1	0	0
Bacterial infection	1	1	0	0	1	1	0	0
C.difficile colitis	1	1	0	0	1	1	0	0
Catheter site infection	0	0	1	1	1	1	0	0
Cellulitis of arm	0	0	1	1	1	1	0	0
Cellulitis of hand	1	1	0	0	1	1	0	0
Clostridium difficile infection	1	1	0	0	1	1	0	0
Community acquired pneumonia	0	0	1	1	1	1	1	1
Diverticulitis	1	1	0	0	1	1	2	2
Gastritis viral	0	0	1	1	1	1	0	0
Gastroenteritis adenovirus	1	1	0	0	1	1	0	0
Groin abscess	1	1	0	0	1	1	0	0
HIV-related dementia	0	0	1	1	1	1	0	0
Infection MRSA	0	0	1	1	1	1	0	0
Infection NOS	0	0	1	1	1	1	1	1
Klebsiella bacteremia	1	1	0	0	1	1	0	0
Maxillary sinusitis	1	1	0	0	1	1	0	0
Methicillin-resistant staphylococcal aureus sepsis	0	0	1	1	1	1	0	0
Obstructive pneumonia	1	1	0	0	1	1	0	0
Otitis media	0	0	1	1	1	1	0	0
Pneumonia MRSA	1	1	0	0	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Prostatitis Escherichia coli	0	0	1	1	1	1	0	0
Purulent bronchitis	0	0	1	1	1	1	0	0
Salmonella infection, unspecified	0	0	1	1	1	1	0	0
Sepsis MRSA	0	0	1	1	1	1	1	2
Septic shock	0	0	1	1	1	1	3	3
Septicemia	0	0	1	1	1	1	0	0
Septicemia staphylococcal	0	0	1	1	1	1	0	0
Serratia infection	0	0	1	1	1	1	0	0
Sinusitis	0	0	1	1	1	1	1	1
Staphylococcal infection	1	1	0	0	1	1	0	0
Urosepsis	1	1	0	0	1	1	0	0
Viral infection	1	1	0	0	1	1	1	1
Viremia	0	0	1	1	1	1	0	0
Wound infection	0	0	1	1	1	1	0	0
Arthritis infective	0	0	0	0	0	0	1	1
Bronchopneumonia	0	0	0	0	0	0	1	1
Clostridium difficile colitis	0	0	0	0	0	0	3	3
Cytomegalovirus viremia	0	0	0	0	0	0	1	1
Febrile cold (excl flu like illness)	0	0	0	0	0	0	1	1
Febrile infection	0	0	0	0	0	0	1	1
GI infection	0	0	0	0	0	0	1	1
Infection pseudomonas aeruginosa	0	0	0	0	0	0	1	1
MRSA colonization	0	0	0	0	0	0	1	1
MRSA wound infection	0	0	0	0	0	0	1	1
Pneumonia aspergillus	0	0	0	0	0	0	1	1
Septic joint	0	0	0	0	0	0	1	1
Suppurative peritonitis, other	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	44 (16.3%)	58	52 (18.6%)	85	96 (17.5%)	143	32 (9.2%)	40
Dyspnea	16	23	19	24	35	47	10	10
Respiratory failure	6	6	11	11	17	17	2	2
COPD exacerbation	4	4	11	20	15	24	5	5
Pleural effusion	3	3	3	4	6	7	3	3
Shortness of breath	4	4	2	3	6	7	0	0
Aspiration pneumonia	2	2	1	1	3	3	1	1
Epistaxis	0	0	3	3	3	3	2	2
Pulmonary hypertension	2	3	1	1	3	4	2	2
Respiratory distress	3	3	0	0	3	3	0	0
COPD	1	1	1	1	2	2	0	0
Dyspnea exertional	1	1	1	1	2	2	0	0
Hypoxemia	0	0	2	2	2	2	0	0
Pneumonitis	0	0	2	2	2	2	0	0
Pulmonary edema	0	0	2	2	2	2	1	1
Pulmonary infiltration	0	0	2	2	2	2	1	1

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Pulmonary thromboembolism	2	2	0	0	2	2	0	0
Acute respiratory failure	0	0	1	1	1	1	0	0
Apnea	1	1	0	0	1	1	0	0
Asthma	1	1	0	0	1	1	0	0
Asthma aggravated	0	0	1	1	1	1	0	0
Bronchitis asthmatic	0	0	1	1	1	1	0	0
Difficulty breathing	0	0	1	1	1	1	0	0
Dyspnea exacerbated	1	1	0	0	1	1	0	0
Exacerbation of asthma	0	0	1	1	1	1	0	0
Hemoptysis	0	0	1	1	1	1	1	3
Hypoxia	0	0	1	1	1	1	3	3
Productive cough	0	0	1	1	1	1	0	0
Pulmonary mass	1	1	0	0	1	1	0	0
Respiratory arrest	1	2	0	0	1	2	0	0
Chronic obstructive pulmonary disease	0	0	0	0	0	0	3	3
Cough	0	0	0	0	0	0	1	1
Hypoventilation	0	0	0	0	0	0	1	1
Pulmonary embolus	0	0	0	0	0	0	1	1
Tachypnea	0	0	0	0	0	0	1	1
General disorders and administration site conditions	35 (13.0%)	43	30 (10.7%)	40	65 (11.8%)	83	36 (10.4%)	46
Chest pain	16	20	10	11	26	31	17	26
Weakness	3	5	7	7	10	12	0	0
Chest pain (non-cardiac)	2	2	4	7	6	9	0	0
Fever	1	1	3	3	4	4	2	2
General malaise	3	3	0	0	3	3	1	1
Death	1	1	1	1	2	2	7	7
Pain	2	2	0	0	2	2	0	0
Sudden cardiac death	1	1	1	1	2	2	1	1
Anasarca	0	0	1	1	1	1	0	0
Central line complication	1	2	0	0	1	2	0	0
Chest discomfort	0	0	1	1	1	1	0	0
Chest pain aggravated	0	0	1	1	1	1	0	0
Chronic fatigue	0	0	1	1	1	1	0	0
Edema of lower extremities	1	2	0	0	1	2	2	2
Fatigue	1	1	0	0	1	1	0	0
Fatigue extreme	1	1	0	0	1	1	0	0
Febrile reaction	0	0	1	1	1	1	0	0
Fever of unknown origin	0	0	1	1	1	1	1	1
Infusion site bleeding	0	0	1	1	1	1	0	0
Multi-organ failure	0	0	1	1	1	1	0	0
Non-cardiac chest pain	0	0	1	1	1	1	1	1
Substernal chest pain	0	0	1	1	1	1	0	0
Sudden death	1	1	0	0	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Swelling	1	1	0	0	1	1	0	0
Edema	0	0	0	0	0	0	1	1
Malaise	0	0	0	0	0	0	1	1
Organ failure	0	0	0	0	0	0	1	1
Thrombus in catheter	0	0	0	0	0	0	1	1
Ulcer	0	0	0	0	0	0	1	1
Vascular disorders	33 (12.2%)	42	27 (9.6%)	28	60 (10.9%)	70	15 (4.3%)	15
Hypotension	15	20	13	14	28	34	6	6
Hematoma	2	2	2	2	4	4	0	0
Orthostatic hypotension	2	2	2	2	4	4	0	0
Deep vein thrombosis leg	3	4	0	0	3	4	0	0
Low output state	3	3	0	0	3	3	0	0
Peripheral arterial disease	2	2	1	1	3	3	0	0
Claudication	2	2	0	0	2	2	1	1
DVT of legs	2	2	0	0	2	2	0	0
Aortic stenosis	0	0	1	1	1	1	0	0
Arterial thrombosis (limbs)	1	1	0	0	1	1	0	0
DVT	0	0	1	1	1	1	1	1
Deep vein thrombosis	0	0	1	1	1	1	0	0
Extremity necrosis	0	0	1	1	1	1	0	0
Hemorrhage, unspecified	1	1	0	0	1	1	0	0
Hemorrhagic shock	1	1	0	0	1	1	0	0
Hypertension	0	0	1	1	1	1	1	1
Hypovolemic shock	1	1	0	0	1	1	2	2
Labile blood pressure	0	0	1	1	1	1	0	0
Peripheral vascular disease	0	0	1	1	1	1	0	0
Shock hemorrhagic	0	0	1	1	1	1	0	0
Subclavian artery thrombosis	1	1	0	0	1	1	0	0
Thromboembolic event	0	0	1	1	1	1	0	0
Bleeding	0	0	0	0	0	0	1	1
Cardiovascular collapse	0	0	0	0	0	0	1	1
Hypertensive emergency	0	0	0	0	0	0	1	1
Ischemia	0	0	0	0	0	0	1	1
Nervous system disorders	29 (10.7%)	37	28 (10.0%)	38	57 (10.4%)	75	27 (7.8%)	32
Syncope	12	15	7	8	19	23	9	13
CVA	2	2	4	4	6	6	2	2
Stroke	3	3	2	2	5	5	3	3
Presyncope	0	0	3	3	3	3	2	2
Carotid artery stenosis	1	1	1	1	2	2	0	0
Dizziness	1	1	1	1	2	2	1	1
Embolic stroke	1	1	1	1	2	2	0	0
Subarachnoid hemorrhage	1	1	1	1	2	2	0	0
Anoxic encephalopathy	0	0	1	1	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ataxia	1	1	0	0	1	1	0	0
Cerebellar infarction	1	1	0	0	1	1	0	0
Cerebral degeneration	1	1	0	0	1	1	0	0
Cerebral infarct	0	0	1	1	1	1	0	0
Cerebrovascular accident	1	1	0	0	1	1	0	0
Disorder brain (chronic)	1	1	0	0	1	1	0	0
Embolic cerebral infarction	0	0	1	1	1	1	0	0
Encephalopathy	0	0	1	1	1	1	1	1
Headache	0	0	1	1	1	1	0	0
Hemorrhagic stroke	0	0	1	1	1	1	0	0
Hepatic encephalopathy	1	1	0	0	1	1	0	0
Hypertensive encephalopathy	0	0	1	1	1	1	0	0
Intracranial hemorrhage	1	1	0	0	1	1	0	0
Ischemic stroke	0	0	1	1	1	1	0	0
Loss of consciousness	1	2	0	0	1	2	1	1
Numbness	0	0	1	2	1	2	0	0
Ophthalmoplegic migraine	0	0	1	1	1	1	0	0
Paresthesia	0	0	1	1	1	1	0	0
Sciatica	1	1	0	0	1	1	0	0
Seizure	1	1	0	0	1	1	0	0
Slurred speech	0	0	1	1	1	1	0	0
Somnolence	1	1	0	0	1	1	0	0
Syncope convulsive	1	1	0	0	1	1	0	0
TIA	0	0	1	1	1	1	2	2
Unresponsive to stimuli	0	0	1	1	1	1	1	1
Vasovagal symptoms	0	0	1	1	1	1	0	0
Weakness left or right side	0	0	1	1	1	1	0	0
Brain injury	0	0	0	0	0	0	1	1
Restless leg syndrome	0	0	0	0	0	0	1	1
Todd's paralysis	0	0	0	0	0	0	1	1
Transient ischemic attacks	0	0	0	0	0	0	2	2
Vocal cord paralysis	0	0	0	0	0	0	1	1
Renal and urinary disorders	33 (12.2%)	41	24 (8.6%)	34	57 (10.4%)	75	20 (5.8%)	22
Acute on chronic renal failure	11	12	9	10	20	22	1	1
Acute renal failure	9	10	7	9	16	19	8	9
Renal insufficiency	9	11	3	4	12	15	5	5
Acute renal insufficiency	0	0	2	2	2	2	0	0
Azotemia	1	1	1	1	2	2	0	0
Chronic kidney disease	1	1	1	1	2	2	0	0
Renal failure	1	1	1	1	2	2	1	1
Acute tubular necrosis	0	0	1	1	1	1	0	0
Chronic renal failure worsened	0	0	1	1	1	1	0	0
End stage renal failure	0	0	1	1	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Hematuria	1	1	0	0	1	1	0	0
Kidney failure	1	1	0	0	1	1	0	0
Lupus nephritis	0	0	1	1	1	1	0	0
Nephrolithiasis	1	1	0	0	1	1	0	0
Renal artery stenosis	1	1	0	0	1	1	0	0
Renal function abnormal	1	1	0	0	1	1	0	0
Uremia	0	0	1	1	1	1	0	0
Urinary retention	0	0	1	1	1	1	2	2
Chronic renal failure	0	0	0	0	0	0	1	1
Kidney disorder	0	0	0	0	0	0	1	1
Renal disease	0	0	0	0	0	0	1	1
Renal failure acute on chronic	0	0	0	0	0	0	1	1
Gastrointestinal disorders	24 (8.9%)	35	31 (11.1%)	49	55 (10.0%)	84	36 (10.4%)	53
GI bleed	6	7	7	7	13	14	9	10
Abdominal pain	3	3	5	6	8	9	2	2
Diarrhea	4	4	1	1	5	5	2	2
Nausea	4	4	1	1	5	5	0	0
Gastritis	3	3	1	1	4	4	1	1
Gastrointestinal bleed	0	0	4	6	4	6	6	8
Vomiting	2	2	2	4	4	6	1	1
Constipation	0	0	3	3	3	3	1	1
Pancreatitis	2	2	1	1	3	3	1	1
Ascites	2	2	0	0	2	2	0	0
Dysphagia	1	1	1	1	2	2	2	2
Emesis	2	2	0	0	2	2	0	0
Esophagitis	0	0	2	2	2	2	0	0
Gastroparesis	0	0	2	2	2	2	1	2
Abdominal bloating	1	1	0	0	1	1	0	0
Abdominal wall hematoma	0	0	1	1	1	1	0	0
Chronic epigastric pain	0	0	1	1	1	1	0	0
Dental caries	0	0	1	1	1	1	0	0
Esophageal spasm	1	1	0	0	1	1	0	0
Esophagitis ulcerative	1	1	0	0	1	1	0	0
Gastric polyps	0	0	1	1	1	1	0	0
Gastritis erosive	0	0	1	1	1	1	0	0
Ileus	0	0	1	1	1	1	0	0
Incarcerated umbilical hernia	0	0	1	1	1	1	0	0
Ischemic colitis	0	0	1	1	1	1	1	2
Melena	1	1	0	0	1	1	0	0
Odynophagia	0	0	1	1	1	1	0	0
Rectal bleeding	0	0	1	3	1	3	1	1
Rectal fistula	0	0	1	1	1	1	0	0
Rectal prolapse	0	0	1	1	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ventral hernia	1	1	0	0	1	1	2	4
Decay dental	0	0	0	0	0	0	1	1
Duodenitis	0	0	0	0	0	0	1	1
Fecal impaction (causing obstruction)	0	0	0	0	0	0	1	1
Gastric ulcer	0	0	0	0	0	0	1	1
Gastric ulcer haemorrhage	0	0	0	0	0	0	1	1
Gastro intestinal bleed	0	0	0	0	0	0	1	1
Gastrointestinal bleeding	0	0	0	0	0	0	2	2
Hematemesis	0	0	0	0	0	0	1	2
Hematochezia	0	0	0	0	0	0	2	2
Mesenteric ischemia	0	0	0	0	0	0	1	1
Reflux esophagitis	0	0	0	0	0	0	1	1
Right upper quadrant pain	0	0	0	0	0	0	1	1
Small bowel obstruction	0	0	0	0	0	0	1	1
Metabolism and nutrition disorders	26 (9.6%)	33	28 (10.0%)	38	54 (9.8%)	71	24 (6.9%)	30
Dehydration	7	9	5	5	12	14	8	8
Hyperglycemia	3	4	5	6	8	10	1	1
Hypoglycemia	4	4	2	2	6	6	2	2
Failure to thrive	2	2	3	4	5	6	1	1
Hypokalemia	2	2	3	3	5	5	3	3
Hypovolemia	2	2	3	3	5	5	0	0
Electrolyte imbalance	2	2	2	2	4	4	0	0
Hypervolemia	2	2	2	2	4	4	0	0
Hyponatremia	1	1	3	3	4	4	4	4
Diabetes	2	2	1	1	3	3	0	0
Hyperkalemia	1	1	2	2	3	3	1	1
Diabetes mellitus loss of control	1	1	1	1	2	2	0	0
Anorexia	0	0	1	1	1	1	0	0
Diabetes mellitus	1	1	0	0	1	1	0	0
Hypercalcemia	0	0	1	1	1	1	0	0
Ketoacidosis (diabetic)	0	0	1	1	1	1	0	0
Volume overload	0	0	1	1	1	1	0	0
Diabetes mellitus inadequate control	0	0	0	0	0	0	1	1
Diabetic ketoacidosis	0	0	0	0	0	0	1	1
Gout	0	0	0	0	0	0	1	1
Gout aggravated	0	0	0	0	0	0	2	2
Gout flare	0	0	0	0	0	0	2	3
Hyperosmolar state	0	0	0	0	0	0	1	1
Hypoglycemic attack	0	0	0	0	0	0	1	1
Surgical and medical procedures	24 (8.9%)	28	29 (10.4%)	34	53 (9.6%)	62	14 (4.0%)	15
Implantable cardioverter defibrillator insertion	4	4	2	2	6	6	0	0
Pacemaker battery replacement	1	1	5	5	6	6	3	3
Cardiac resynchronisation therapy	2	2	2	2	4	4	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Heart transplant	1	1	3	3	4	4	2	2
Cardiac catheterization	3	5	0	0	3	5	0	0
Implantable defibrillator replacement	0	0	3	3	3	3	0	0
Amputation	0	0	2	2	2	2	0	0
Cardiac ablation	1	1	1	1	2	2	0	0
Cardiac resynchronization therapy	0	0	2	2	2	2	0	0
Cardioversion	1	1	1	1	2	2	0	0
Cholecystectomy	0	0	2	2	2	2	0	0
Foot surgery	1	1	1	1	2	2	1	1
Inguinal hernia repair	1	1	1	1	2	2	0	0
Abdominal hernia repair	1	1	0	0	1	1	0	0
Brachytherapy	1	1	0	0	1	1	0	0
Cardiac pacemaker revision	1	1	0	0	1	1	0	0
Central line placement	0	0	1	1	1	1	0	0
Colostomy closure	1	1	0	0	1	1	0	0
Epicardial lead placement	1	1	0	0	1	1	1	1
Gallbladder operation	0	0	1	1	1	1	0	0
Gastric bypass	0	0	1	1	1	1	0	0
Implantable defibrillator insertion	1	1	0	0	1	1	1	1
Incisional drainage	1	1	0	0	1	1	0	0
Knee total replacement	0	0	1	1	1	1	0	0
Mitral valve replacement	0	0	1	1	1	1	0	0
Neuroma removal	1	1	0	0	1	1	0	0
Parotidectomy	0	0	1	1	1	1	0	0
Polypectomy	1	1	0	0	1	1	0	0
Stent placement	1	1	0	0	1	1	0	0
Total hip replacement	1	1	0	0	1	1	0	0
Total knee replacement	0	0	1	2	1	2	0	0
Tricuspid valve repair	0	0	1	1	1	1	0	0
Arteriovenous graft	0	0	0	0	0	0	1	1
Catheterization cardiac	0	0	0	0	0	0	2	2
Hospitalization NOS	0	0	0	0	0	0	1	1
Knee surgery NOS	0	0	0	0	0	0	1	1
Left ventricular assist device insertion	0	0	0	0	0	0	1	1
Ventricular assist device insertion	0	0	0	0	0	0	1	1
Injury, poisoning and procedural complications	18 (6.7%)	21	16 (5.7%)	19	34 (6.2%)	40	15 (4.3%)	16
Lead dislodgement	2	2	2	2	4	4	0	0
Hip fracture	0	0	3	3	3	3	1	1
Bleeding postoperative	1	1	1	1	2	2	0	0
Device malfunction	0	0	2	2	2	2	0	0
Fall	2	2	0	0	2	2	2	2
Head injury	0	0	2	2	2	2	0	0
Lead conductor fracture	2	2	0	0	2	2	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Subdural hematoma	2	2	0	0	2	2	2	2
Accidental overdose	1	1	0	0	1	1	0	0
Ankle fracture	1	1	0	0	1	1	0	0
Cardiac pacemaker malfunction	0	0	1	1	1	1	0	0
Compression fracture	0	0	1	1	1	1	0	0
Contusion	0	0	1	1	1	1	0	0
Device lead damage	0	0	1	1	1	1	0	0
Device lead issue	1	1	0	0	1	1	0	0
Digoxin toxicity	1	1	0	0	1	1	3	3
Femur fracture	0	0	1	1	1	1	0	0
Fracture rib	1	1	0	0	1	1	0	0
Fractured hip	1	1	0	0	1	1	0	0
Fractured nose	1	1	0	0	1	1	0	0
Fractured pelvis NOS	1	1	0	0	1	1	0	0
Hematoma traumatic	1	1	0	0	1	1	0	0
Humerus fracture	0	0	1	1	1	1	0	0
Medical device complication	0	0	1	1	1	1	0	0
Migration of implant	1	1	0	0	1	1	0	0
Motor vehicle accident	1	1	0	0	1	1	0	0
Pneumothorax traumatic	1	1	0	0	1	1	0	0
Skin avulsion injury	0	0	1	1	1	1	0	0
Subdural haemorrhage	0	0	1	1	1	1	0	0
Chemical pneumonitis	0	0	0	0	0	0	1	1
Device complication	0	0	0	0	0	0	5	5
Overdose accidental	0	0	0	0	0	0	1	1
Sciatic nerve injury	0	0	0	0	0	0	1	1
Musculoskeletal and connective tissue disorders	11 (4.1%)	14	13 (4.6%)	13	24 (4.4%)	27	16 (4.6%)	17
Back pain	0	0	2	2	2	2	1	1
Chest wall pain	1	1	1	1	2	2	0	0
Degenerative joint disease	1	1	1	1	2	2	1	1
Arthritis	1	1	0	0	1	1	1	1
Arthritis single joint	0	0	1	1	1	1	0	0
Back pain aggravated	1	2	0	0	1	2	0	0
Charcot's joint	0	0	1	1	1	1	0	0
Groin pain	0	0	1	1	1	1	0	0
Hemarthrosis involving lower leg	1	1	0	0	1	1	0	0
Lumbar spinal stenosis	0	0	1	1	1	1	0	0
Lupus erythematosus	0	0	1	1	1	1	1	2
Muscle necrosis	1	1	0	0	1	1	0	0
Musculoskeletal chest pain	1	1	0	0	1	1	0	0
Neck pain	1	1	0	0	1	1	1	1
Olecranon bursitis	0	0	1	1	1	1	0	0
Osteoarthritis knee	0	0	1	1	1	1	0	0

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Polymyositis	1	1	0	0	1	1	0	0
Pseudogout	0	0	1	1	1	1	0	0
Rheumatoid arthritis	1	1	0	0	1	1	0	0
Rotator cuff tear	1	1	0	0	1	1	1	1
Scleroderma	0	0	1	1	1	1	0	0
Shoulder blade pain	1	1	0	0	1	1	0	0
Spinal column stenosis	1	1	0	0	1	1	0	0
Cervical spondylosis	0	0	0	0	0	0	1	1
Foot pain	0	0	0	0	0	0	1	1
Joint instability	0	0	0	0	0	0	1	1
Knee pain	0	0	0	0	0	0	1	1
Low back pain	0	0	0	0	0	0	1	1
Osteoarthritis knees	0	0	0	0	0	0	1	1
Pain in joint involving lower leg	0	0	0	0	0	0	1	1
Shoulder pain	0	0	0	0	0	0	1	1
Spinal stenosis NOS	0	0	0	0	0	0	1	1
Spondylolisthesis	0	0	0	0	0	0	1	1
Blood and lymphatic system disorders	13 (4.8%)	14	10 (3.6%)	13	23 (4.2%)	27	14 (4.0%)	20
Anemia	11	12	8	10	19	22	11	12
Thrombocytopenia	1	1	1	1	2	2	1	1
Anemia microcytic	1	1	0	0	1	1	0	0
Leukocytosis	0	0	1	1	1	1	0	0
Neutropenia	0	0	1	1	1	1	0	0
Anemia aggravated	0	0	0	0	0	0	1	1
Hemolysis	0	0	0	0	0	0	1	5
Neutropenic fever	0	0	0	0	0	0	1	1
Investigations	10 (3.7%)	10	5 (1.8%)	6	15 (2.7%)	16	3 (0.9%)	4
Serum creatinine increased	2	2	1	2	3	4	0	0
Transplant evaluation	2	2	0	0	2	2	0	0
Anticoagulation drug level above therapeutic	1	1	0	0	1	1	0	0
Blood culture positive	1	1	0	0	1	1	0	0
Blood glucose fluctuation	0	0	1	1	1	1	0	0
INR	0	0	1	1	1	1	0	0
INR increased	1	1	0	0	1	1	0	0
International normalized ratio decreased	0	0	1	1	1	1	0	0
Mediastinoscopy	1	1	0	0	1	1	0	0
Pulmonary arterial pressure increased	1	1	0	0	1	1	1	1
QT interval prolonged	1	1	0	0	1	1	0	0
Ventricular filling pressure increased	0	0	1	1	1	1	0	0
Blood sugar abnormal	0	0	0	0	0	0	1	1
INR decreased	0	0	0	0	0	0	1	1
Urinary output diminished	0	0	0	0	0	0	1	1
Psychiatric disorders	7 (2.6%)	7	7 (2.5%)	7	14 (2.5%)	14	6 (1.7%)	7

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Acute mental status changes	3	3	7	7	10	10	4	4
Agitation	1	1	0	0	1	1	0	0
Delirium toxic	1	1	0	0	1	1	0	0
Panic attack	1	1	0	0	1	1	0	0
Suicidal ideation	1	1	0	0	1	1	0	0
Mental status changes	0	0	0	0	0	0	2	2
Withdrawal syndrome	0	0	0	0	0	0	1	1
Hepatobiliary disorders	6 (2.2%)	8	7 (2.5%)	8	13 (2.4%)	16	2 (0.6%)	3
Acute cholecystitis	4	4	0	0	4	4	0	0
Cholecystitis	1	1	3	3	4	4	0	0
Cholelithiasis	2	2	0	0	2	2	2	2
Gallstones	0	0	1	1	1	1	1	1
Hepatic fibrosis	0	0	1	2	1	2	0	0
Injury to liver	1	1	0	0	1	1	0	0
Liver disorder	0	0	1	1	1	1	0	0
Portal hypertension	0	0	1	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.9%)	7	4 (1.4%)	5	9 (1.6%)	12	5 (1.4%)	5
Lung cancer	2	2	1	1	3	3	1	1
Large cell lung cancer	0	0	1	1	1	1	0	0
Lung nodule	0	0	1	1	1	1	0	0
Lymphocytic leukemia	0	0	1	1	1	1	0	0
Myelodysplastic syndrome	1	1	0	0	1	1	0	0
Ovarian cancer	1	1	0	0	1	1	0	0
Prostate cancer metastatic	0	0	1	1	1	1	0	0
Skin cancer	1	1	0	0	1	1	0	0
Small cell carcinoma of the lung	1	2	0	0	1	2	0	0
Adenoma	0	0	0	0	0	0	1	1
Breast cancer	0	0	0	0	0	0	1	1
Esophageal cancer	0	0	0	0	0	0	1	1
Lymphoma	0	0	0	0	0	0	1	1
Endocrine disorders	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	1 (0.3%)	1
Adrenal insufficiency	1	1	0	0	1	1	0	0
Hypothyroidism	1	1	0	0	1	1	1	1
Myxedema	0	0	1	1	1	1	0	0
Immune system disorders	2 (0.7%)	2	1 (0.4%)	1	3 (0.5%)	3	0 (0.0%)	0
Amyloidosis	1	1	0	0	1	1	0	0
Heart transplant rejection	0	0	1	1	1	1	0	0
Transplant rejection	1	1	0	0	1	1	0	0
Skin and subcutaneous tissue disorders	0 (0.0%)	0	3 (1.1%)	3	3 (0.5%)	3	3 (0.9%)	4
Diabetic ulcer	0	0	1	1	1	1	0	0
Foot ulcer	0	0	1	1	1	1	0	0
Venous stasis ulcer	0	0	1	1	1	1	0	0
Decubitus ulcer	0	0	0	0	0	0	1	1

Table 34. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Rash	0	0	0	0	0	0	1	2
Skin thinning of	0	0	0	0	0	0	1	1
Benign prostatic hypertrophy	0	0	1	1	1	1	0	0
Reproductive system and breast disorders	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	3 (0.9%)	3
Enlarged prostate	0	0	0	0	0	0	1	1
Postmenopausal bleeding	0	0	0	0	0	0	1	1
Vaginal bleeding	0	0	0	0	0	0	1	1

Adverse Device Events

Table 35. Unanticipated or Serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Unanticipated Serious Adverse Device Events	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	0 (0.0%)	0
Serious Adverse Device Events	2 (0.7%)	2	0 (0.0%)	0	2 (0.4%)	2	0 (0.0%)	0

Unanticipated Serious Adverse Device Events

There was one event during Part 1 reported as a USADE by the investigator but determined not to be serious or device system related by the CEC which reviewed the event on 27 Jun 2009. There were no additional USADEs over Part 2 of the clinical trial.

Serious Adverse Device Events

The two SADEs that occurred during Part 1 were hemoptysis during the implant procedure and an in-situ thrombosis during the right heart catheterization procedure. Both patients were treated and recovered without sequela. There were no additional SADEs over Part 2 of the clinical trial.

Long-term Data from the CardioMEMS US Post-Approval Study

Summary of the Post-Approval Study Methods

Study Objective

The objective of the CardioMEMS US Post-Approval Study (PAS) was to confirm the safety and effectiveness of the CardioMEMS™ HF System in patients with New York Heart Association (NYHA) Class III heart failure (HF) (a minimum of 35% of the enrolled patients were to be women) who experienced a heart failure hospitalization (HFH) in the previous year.

Study Design

The PAS was a prospective, non-randomized, open-label, multi-center, post-approval study designed to characterize the use of the CardioMEMS HF System as a condition of the U.S. Food and Drug Administration (FDA).

Study Population

Subjects enrolled in the PAS were male and female patients of at least 18 years of age with NYHA Class III heart failure who were hospitalized for HF in the previous 12 months, who met all eligibility criteria, and provided written informed consent. A prerequisite of the study was that at least 35% of the enrolled patients were to be women.

Data Source

Part 11 compliant electronic case report forms (eCRFs) were utilized. Study site staff entered the information required by the protocol onto eCRFs using a validated system that conforms to FDA requirements for electronic data capture. Only authorized site personnel were permitted to enter the CRF data through the electronic data capture (EDC) system deployed by the Sponsor.

Key Study Endpoints

The primary safety endpoints were (1) freedom from device/system-related complications (DSRCs) at 2 years and (2) freedom from pressure sensor failure at 2 years. The primary effectiveness endpoint was the annualized HFH rate at 1 year compared to the annualized HFH rate for 1 year prior to implant.

Total number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of 1200 subjects were implanted (enrolled) with the CardioMEMS sensor at 104 investigational sites in the United States. An additional 14 subjects had attempted implants that were not successful and therefore were not enrolled in the study. These subjects were followed through 30 days per the study protocol before exiting and are included in appropriate analyses. All enrolled subjects were followed for 24 months or until they exited the study. The number of patients who completed 24 months of follow-up was 710 of the 1200 patients enrolled (59.2%).

Study visits and length of follow-up

Following sensor implant, follow-up visits were scheduled at 1 month, 6 months, 12 months, 18 months, and 24 months. All subjects were followed until completion of their 24-month visit or withdrawal from the study. The average length of patient follow-up was 18.7 months.

Summary of the Post-Approval Study Results

Final Safety Findings

The pre-specified performance goals for each of the primary safety endpoints were that at least 80% of the patients were to be free from DSRC and at least 90% of patients were to be free of sensor failure at 24 months. The results in the table below show that freedom from DSRC at 24 months was 99.6% (1209/1214) with a lower confidence bound of 99.0% (0.990), exceeding the pre-specified performance goal of 80%. The results (table below) show that freedom from pressure sensor failure at 24 months was 99.9% with a lower confidence bound of 99.5%, exceeding the pre-specified performance goal of 90%. Both hypotheses had to be met in order to declare the study successful. Both primary safety endpoints were met.

Table 36. Primary Safety Endpoints

Safety Endpoint	Kaplan- Meier Estimate	Proportion	Lower Confidence Limit [76]	p-value [77]
Freedom from DSRC [78]	99.6%	99.6% (1209/1214)	99.0%	p < 0.0001
Freedom from Pressure Sensor Failure [79]	99.9%	99.9% (1199/1200)	99.5%	p < 0.0001

Final Effectiveness Findings

The primary effectiveness endpoint for this study compares the annualized HFH rate (including recurrent events) at 12 months post-implant with the rate (including recurrent events) 12 months prior to implant. All follow-up through 12 months post-implant or until subject exits the study were included in the analysis. All subjects who were consented and successfully implanted with a pressure sensor, regardless of study completion status were included in the analysis.

The table below denotes the total number of HFHs for all patients in the year prior to implant (1600 HFHs) and for one year after CardioMEMS sensor implant (628 HFHs) for all successfully implanted subjects (n=1200). The HFH rate prior to sensor implant was 1.249 HFHs per patient year. After sensor implant, the rate of HFHs was reduced to 0.535 HFHs per patient year. This is a reduction of 57% in HFHs after treatment using the CardioMEMS sensor (p<0.0001).

Table 37. Annualized HFH Rate

	One Year prior to Implant [80]	One Year after Implant [81]	Hazard Ratio (95% CI) p-value [82]
Number of HFHs	1600	628	0.43 (0.39, 0.47) p<0.0001
One Year HFH Rate [83]	1.249	0.535	

As noted in the previous section, the CHAMPION trial was not powered to show statistical significance for gender. Because of this, the PAS had a requirement to enroll at least 35% women and a pre-specified effectiveness analyses of annualized HFH rate at one year compared the year prior to implant was evaluated in both women and men. The goal to enroll at least 35% women was met and approximately 38% of patients enrolled in the PAS were women. Note that the rate of HFH at one year in females (0.513) is comparable to that in males (0.553). This is important as it demonstrates that female subjects have a similar response to the use of CardioMEMS as male subjects.

Table 38. Primary Effectiveness by Sex

Sex	One Year prior to Implant Events (Rate [84])	One Year after Implant Events (Rate [85])	Hazard Ratio (95% CI), p-value [86]	Interaction p-value
Male (N=748)	970 (1.214)	398 (0.553)	0.46 (0.40, 0.52), p<0.0001	0.1587
Female (N=452)	630 (1.319)	230 (0.513)	0.39 (0.33, 0.46), p<0.0001	

Study Strength and Weaknesses

The CardioMEMS US PAS is the first clinical study to produce long-term data on the CardioMEMS HF System. The PAS met both of its primary safety endpoints and demonstrated a large reduction (57%) in HFHs at one year. In comparison to the pivotal CHAMPION trial, where freedom from DSRC was 98.6% with a lower 95% confidence limit of 97.3%, the CardioMEMS US PAS freedom from DSRC of 99.6% with a lower confidence limit of 99.0%, exceeded the pre-specified performance goal. In the CardioMEMS US PAS, one patient out of 1200 implanted patients (0.1%) had sensor failure, indicating a freedom from pressure sensor failure at 24 months of 99.9%, which is similar to the 100% freedom from sensor failure observed during the CHAMPION trial.

[76] Lower Exact 95% Clopper-Pearson confidence limit.
[77] DSRC p-value tests the one-sided binomial proportion is greater than 80% with 95% confidence, and Pressure Sensor Failure p-value tests the one-sided binomial proportion is greater than 90% with 95% confidence.
[78] Denominator includes all subjects in the Safety Population.
[79] Denominator includes all subjects in the Effectiveness Population.
[80] Includes all CEC adjudicated HFHs with an admission date on the date of implant and through 390 days prior to date of implant.
[81] Includes all CEC adjudicated HFHs with an admission date after the implant procedure discharge date through 390 days after the date of implant.
[82] Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.
[83] HFH Rate is an annualized rate estimated from the Andersen-Gill model.
[84] HFH Rate is an annualized rate estimated from the Andersen-Gill model.
[85] HFH Rate is an annualized rate estimated from the Andersen-Gill model.
[86] Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.

A limitation of the CardioMEMS US PAS single arm design is that there is not a direct comparator provided within the study population for outcomes. However, results from the CardioMEMS US PAS are supported by results from the CHAMPION trial and MEMS-HF study (first CardioMEMS study outside the US) [87]. In the CHAMPION pivotal trial, a 33% relative risk reduction in HFH was observed in treatment patients versus control over an 18-month average follow-up period [88]. Results similar to the CardioMEMS US PAS have been reported from the MEMS-HF study, where a 62% reduction in the HFH rate (HR:0.38, CI:0.31, 0.48; p<0.0001) was observed at 12 months. The CardioMEMS US PAS has demonstrated that the CardioMEMS HF System study is safe (99.6% freedom from DSRCs and 99.9% freedom from sensor failure) and effective (57% reduction in HFH), thus demonstrating the long-term safety and efficacy of the CardioMEMS HF system.

Cleaning

- Do not submerge the system in water.
- Unplug the electronics unit prior to cleaning.
- To clean the LCD screen, make sure the electronics unit is in the power off mode. Unplug the monitor from the power source before cleaning. Stand away from the LCD monitor and spray cleaning solution onto a clean lint free cloth. Without applying excessive pressure, clean the screen with a slightly dampened cloth.
- To clean the antenna and electronics enclosure, wipe clean with a slightly damp cloth using soap, mild detergent, or water. Make sure parts are dry before turning the electronics unit on.
- Follow the normal biohazard routine per hospital protocol followed for any contaminated parts.

Storage

- Store the system within the environmental limits stated in the Environmental Information section.
- Excessive vibration, impact, or rough handling may damage the system.
- Exposing the screen to rain, water, moisture or sunlight may severely damage the system.
- To avoid potential damage caused by lightning, unplug the electronics unit from any unprotected outlet during electrical storms.

User/Owner Responsibility

The Hospital Electronics System and the authorized replacement parts are designed to work as described in this manual. The user(s) of this equipment should not use parts that have failed, exhibit excessive wear, are contaminated, or otherwise ineffective. Owner's responsibilities:

- Replacement of components as required for safe and reliable operation
- Replacement of ineffective parts with parts supplied by the manufacturer

The system should not be modified. The user of this equipment is responsible for reading, understanding, and following the Warning and Precaution statements presented within this manual.

Electromagnetic Interference and Electromagnetic Compatibility

This section provides a brief overview of Electromagnetic Interference and Electromagnetic Compatibility guidance associated with the use of the CM3000.

Table 39. Electromagnetic Emissions

Guidance and manufacturer's declaration – electromagnetic emissions		
The electronics unit is intended for use in the electromagnetic environment specified below. The customer or the user of the electronics unit should assure that it is used in such an environment.		
Emissions test	**Compliance**	**Electromagnetic environment - guidance**
RF emissions CISPR 11 CISPR 22	Class A, Group 2 Class B	The electronics unit must emit electromagnetic energy in order to perform its intended function. Nearby electronic equipment may be affected. The electronics unit is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Class A	
Voltage fluctuations/ Flicker emissions IEC 61000-3-3	Complies	

Table 40. Electromagnetic Immunity

Guidance and manufacturer's declaration – electromagnetic immunity			
The electronics unit is intended for use in the electromagnetic environment specified below. The customer or the user of the electronics unit should assure that it is used in such an environment.			
Immunity Test	**IEC 60601 Test level**	**Compliance level**	**Electromagnetic environment - guidance**
Electrostatic discharge (ESD) IEC 61000-4-2	±8 kV contact ±15 kV air	±8 kV contact ±15 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.

[87] Angermann CE, Assmus, B, Anker, SD, ET AL. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). *European Journal of Heart Failure*. 2020. doi: 10.1002/ejhf.1943.

[88] Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomized trial. *Lancet*. 2016;387:453-61.

Table 40. Electromagnetic Immunity

Guidance and manufacturer's declaration – electromagnetic immunity

The electronics unit is intended for use in the electromagnetic environment specified below. The customer or the user of the electronics unit should assure that it is used in such an environment.

Immunity Test	**IEC 60601 Test level**	**Compliance level**	**Electromagnetic environment - guidance**
Electrical fast transient/burst IEC 61000-4-4	±2 kV for power supply lines ±1 kV for input/output lines	±2 kV for power supply lines ±1 kV for input/output lines	Mains power quality should be that of a typical commercial or hospital environment
Surge IEC 61000-4-5	±1 kV line(s) to line(s) ±2 kV line(s) to earth	±1 kV line(s) to line(s) Not applicable	Mains power quality should be that of a typical commercial or hospital environment
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	0% U_T [89] (100% dip in U_T) for 0.5 cycle	0% U_T (100% dip in U_T) for 0.5 cycle	Mains power should be that of a typical commercial or hospital environment. If the user of the electronics unit requires continued operation during power mains interruptions, it is recommended that the electronics unit be powered from an uninterruptible power supply or a battery.
	0% U_T (100% dip in U_T) for 1 cycle	0% U_T (100% dip in U_T) for 1 cycle	
	70% U_T (30% dip in U_T) for 25 cycles	70% U_T (30% dip in U_T) for 25 cycles	
	0% U_T (100% dip in U_T) for 5 sec	0% U_T (100% dip in U_T) for 5 sec	
Power frequency (50/60 Hz) Magnetic field IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
Conducted RF IEC 61000-4-6	3 Vrms 150 kHz to 80 MHz ISM Bands	3 Vrms 6 Vrms	Portable and mobile RF communication equipment should be no closer to any part of the electronics unit, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. **Recommended separation distance** $d = 1.2\sqrt{P}$ $d = 1.2\sqrt{P}$ **80 MHz to 800 MHz** $d = 2.3\sqrt{P}$ **800 MHz to 2.7 GHz** where **P** is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey, should be less than the compliance level in each frequency range [90]. Interference may occur in the vicinity of equipment marked with the following symbol: 
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.7 GHz	3 V/m	

Electromagnetic site survey- Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the electronics unit is used exceeds the applicable RF compliance level above, the electronics unit should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as reorienting or relocating the electronics unit.

[89] U_T is the a.c. mains voltage level prior to application of the test level.

[90] Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

Table 41. Recommended separation distances between portable and mobile RF communications equipment and the electronics unit

The electronics unit is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the electronics unit can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the electronics unit as recommended below, according to the maximum output power of the communications equipment.

Rated Maximum output power of transmitter (W)	**Separation distance according to frequency of transmitter** [91]		
	150 kHz to 80 MHz **d = 1.2 √P**	**80 MHz to 800 MHz** [92] **d = 1.2 √P**	**800 MHz to 2,7 GHz** **d = 2.3 √P**
0.01	0.12 m	0.12 m	0.23 m
0.1	0.38 m	0.38 m	0.73 m
1	1.20 m	1.20 m	2.30 m
10	3.79 m	3.79 m	7.27 m
100	12.00 m	12.00 m	23.00 m

For transmitters rated at a maximum output not listed above, the recommended separation distance (**d)** in meters can be estimated using the equation applicable to the frequency of the transmitter, where **P** is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

For two electronics units operating simultaneously and in proximity test results indicate that the separation distance should be greater than 4 meters (13 feet and 2 inches).

FCC Statement

This device complies with Part 18 of the FCC rules.

The PA Sensor is approved for wireless transmission under FCC ID number R3PCS-A-000051. The sensor complies with Part 15 of the FCC Rules. Operation is subject to the following two conditions: (1) this device may not cause harmful interference and (2) this device must accept any interference received, including interference that may cause undesired operation.

This product operates in the 2.4-2.4835 GHz band with an RF output power of less than 0.04 mW EIRP.

EU REACH SVHC Disclosure

Current Candidate List (as published July 2014)

REACH - the regulation concerning Registration, Evaluation, Authorization and Restriction of Chemicals - is a law within the European Union. REACH applies to all EU manufacturers, importers and users of chemical substances, as well as EU producers, importers and suppliers of articles such as finished goods, parts and components.

Article 33 of REACH requires us to provide information about certain “substances of very high concern” (“SVHCs”) if any SVHCs are present in a concentration of more than 0.1% of the weight of an article that we supply in the EU.

Based on information currently available, no substances from the SVHC candidate list are present in our products as described by Article 33, except as follows:

(DEHP, bis(2-ethyl(hexyl)phthalate), CAS nr.: 117-81-7; EC nr. 204-211-0).

DEHP is found in the following component(s):

Table 42. Component

Component	**Part**	**Amount Present**
Rigid Antenna	CS-000132	Less than 0.8% w/w (weight of substance/weight of product)

As a result, there are no restrictions for the user of the rigid antenna in this application.

WEEE Compliance Statement

The 2012/19/EU Directive on Waste Electrical and Electronic Equipment (the WEEE Directive) states that new equipment placed on the market within the European Union must comply with the WEEE directive which aims to ensure that products can be easily broken down or recycled at the end of the life cycle. The manufacturer is committed to complying with the EU WEEE directive. Products put on the market are required to be marked with the crossed through recycling bin symbol and something that identifies that it was put on the market on or after this date.

System Specifications

Electrical Characteristics

Power

- Power Supply: Input: Class II 100-240V, 50-60 Hz, Output: 12 VDC, 6A
- Manufacturer part number: CS-001301
- Only use power cord (CM3020) supplied by the manufacturer

Radiofrequency (RF) Characteristics

- Transmitted Electrical Power: < 1 mW e.r.p.
- Operating Frequency: 30-37.5 MHz. Under normal operating conditions the measurement bandwidth is approximately 1 MHz within the operating frequency range.

[91] These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

[92] At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

Mechanical Characteristics

Main Unit

- Weight: approximately 8 pounds
- Dimensions: Height:11.5 inches Width: 10.5 inches Length: 5.5 inches
- Product Life: 5 years
- I/O: 2 USB, RS-232
- Printer: FP-900064
- Optional WIFI adapter: CM3040

Display

- Touchscreen: Resistive
- Brightness: approximately 250 cd/m2
- Resolution: 800 x 480, color

Antenna

- Weight: approximately 4 pounds
- Diameter: 9 inches
- Cable: Reference manufacturer's part number CS-000135

Environmental Information

- Operation: 5° to 40°C (41° to 104°F), 15% to 93% humidity (non-condensing), 700-1060 hPa (Electronics), 800-1150 hPa (implanted sensor)
- Transportation: -25° to 70°C (-13° to 158°F) and up to 93% humidity (non-condensing)
- Storage: -25° to 70°C (-13° to 158°F) and up to 93% humidity (non-condensing)

Classification

- Class II equipment
- Type BF insulation
- Ordinary Equipment IP 21
- Continuous Use

Testing

System Testing

- System Accuracy (under typical environmental conditions): +/- 2 mmHg at baseline and +/-3% of difference between measured pressure and baseline
- System Accuracy: +/-4 mmHg over the range of environmental conditions
- The CM3000 was issued an ETL/cETL Listing Mark

Safety Testing

- IEC 60601-1
- ANSI ES 60601-1
- CENELEC EN 60601-1
- CAN/CSA-C22.2 No. 60601-1

EMI/EMC Testing

- CENELEC EN 60601-1-2
- ETSI EN 301 489-1

Wireless Testing

- FCC part 18 (Electronics System)
- FCC part 15 (Sensor)
- ETSI EN 301 489-3
- ETSI EN 302 510
- CISPR 11
- CISPR 22

Software

This device contains open source software. Source code is available upon request.

Technical Support

In North America:

For Merlin.net™ PCN patients, telephone Technical Support is available Monday through Friday (8AM to 8PM Eastern Standard Time). For clinicians, telephone Technical Support is available 24-hours a day.

For Merlin.net Patient Care Network support:

- 1 877 696 3754 (1 877 MY MERLIN) (toll-free within North America)

In Europe:

Telephone Technical Support is available Monday through Friday (8:00 to 17:00 Central European Time).

- +46 8 474 4756 (Sweden) (Support in English and Swedish)

St. Jude Medical maintains 24-hour phone lines for technical questions and support:

- 1 818 362 6822
- 1 800 722 3774 (toll-free within North America)
- + 46 8 474 4147 (Sweden)

For additional assistance, call your local St. Jude Medical representative.

Symbols

The symbols below and harmonized symbols may be found on the product or product label. For harmonized symbols, refer to the Universal Symbols Glossary at https://manuals.sjm.com.

Symbol	Description
	Reorder number
	Follow instructions for use on this website
	Keep dry
	Date of Manufacture
	Manufacturer
	Temperature limitations
	Humidity limitation
	Serial number
	Made in USA
	Momentary pushbutton
	Quantity, package contents
	Do not use if package is damaged
	The device contains a battery and the label is affixed to this device in accordance with European Council Directives 2002/96/EC and 2006/66/EC. These directives call for separate collection and disposal of electrical and electronic equipment and batteries. Sorting such waste and removing it from other forms of waste lessens the contribution of potentially toxic substances into municipal disposal systems and into the larger ecosystem. Return the device to St. Jude Medical at the end of its operating life.
	Direct current

Symbol	Description
	Federal Communication Commission Number (FCC ID: #)
	Non-ionizing radiation
	Type BF Patient Applied Part
IP21	IEC 60529 Ingress Protection Level
	Class II equipment
	Manufacturing Facility
	Australian Communications and Media Authority (ACMA) and New Zealand Radio Spectrum Management (RSM) Regulatory Compliance Mark (RCM)
℞ ONLY	For prescription use only
ETL CLASSIFIED c ETL us Intertek 4002966	Conforms to AAMI Std ES60601-1 Certified to CAN/CSA std C22.2 No. 60601-1

St. Jude Medical
387 Technology Circle NW
Atlanta, GA 30313 USA
+1 866 240 3335

St. Jude Medical
One St. Jude Medical Drive
St. Paul, MN 55117-9913 USA

St. Jude Medical
387 Technology Circle NW, Suite 500
Atlanta, Georgia 30313 USA

sjm.com

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ST. JUDE MEDICAL™

CardioMEMS™ HF System

PA Sensor and Delivery System

Model CM2000

User's Manual

ST. JUDE MEDICAL

- Do not attempt to use the device before also reading and fully understanding the System Guide.
- Carefully inspect all product packaging for damage or defects prior to use. Do not use product if you see any indication of damage or breach of the sterile barrier.
- This device is supplied sterile for single use only. After use, dispose of the Delivery System. Do not resterilize.
- Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician.

Contents

Description

The CardioMEMS™ HF System provides pulmonary artery (PA) hemodynamic data used for the monitoring and management of heart failure (HF) patients. The system measures changes in PA pressure which physicians use to initiate or modify heart failure treatment.

The system includes the following components:

- Implantable wireless sensor with delivery catheter
- Patient or Hospital Electronics System
- Patient database

The wireless sensor is designed for permanent implantation into the distal pulmonary artery. Once implanted, the CardioMEMS PA Sensor provides non-invasive hemodynamic data that is collected in the physician's office, clinic, hospital, or the patient's home. The data provided by the system includes:

- PA pressure waveform
- Systolic, Diastolic, and Mean PA pressure
- Heart Rate

This hemodynamic data is transmitted to a secure website that serves as the patient database so that PA monitoring information is available at all times through the Internet. Changes in PA pressure can be used in conjunction with heart failure signs and symptoms to guide adjustments to medications.

For information on the operation of the CardioMEMS HF System, please refer to the System Guide. For information on operation of the patient database, please refer to the Merlin.net™ Patient Care Network Heart Failure Management Application Help manual. For clinical study information, please refer to that section of this guide.

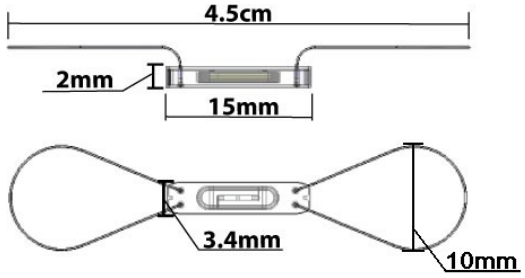


Figure 1. PA Sensor

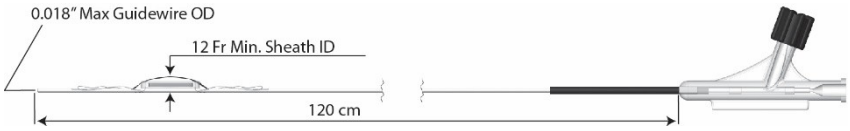


Figure 2. PA sensor and delivery system

Table 1. Device model numbers

Device	Model number
PA Sensor and Delivery System	CM2000
Patient Electronics System	CM1100
Hospital Electronics System	CM3000

Indications

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.

Contraindications

The CardioMEMS™ HF System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one month post implant.

Clinical Considerations for Patient Selection

An elevated natriuretic peptide level is defined as an NT-proBNP level ≥ 1000 pg/ml or a BNP level ≥ 250 pg/ml. Thresholds are dependent on left ventricular ejection fraction and body mass index, using a 4%[1] reduction per BMI unit over 25 kg/m², as listed in the table below.

Table 2. NT-proBNP and BNP Thresholds According to LVEF and BMI

BMI (kg/m²)	NT-proBNP Threshold (pg/ml)		BNP Threshold (pg/ml)	
	LVEF ≤ 40%	LVEF > 40%	LVEF ≤ 40%	LVEF > 40%
≤ 25	1000	700	250	175
26	955	668	238	167
27	911	638	227	159
28	870	608	216	151
29	830	581	206	144
30	792	554	197	137
31	756	529	187	130
32	722	504	178	124
33	689	481	170	118
34	657	459	162	112
35	627	438	154	107
36	599	418	147	101
37	571	399	140	96
38	545	380	133	92
39	520	363	126	87
40	496	346	120	83
41	473	330	114	79
42	452	315	109	75
43	431	300	103	71
44	411	286	98	67
45	392	273	94	64
46	374	260	89	60
47	357	248	84	57
48	340	236	80	54
49	324	225	76	51
50	309	215	72	49

The following patients may not be appropriate for implantation of the CardioMEMS™ HF System:

- Patients with an active infection.
- Patients with a history of recurrent (>1) pulmonary embolism or deep vein thrombosis
- Patients unable to tolerate a right heart catheterization (RHC).
- Patients with a Glomerular Filtration Rate (GFR) <25 ml/min who are non-responsive to diuretic therapy or who are on chronic renal dialysis.
- Patients with congenital heart disease or mechanical right heart valve(s)
- Patients with known coagulation disorders.
- Patients with a hypersensitivity or allergy to aspirin, and/or clopidogrel.
- Patients who have undergone implantation of a Cardiac Resynchronization Device (CRT) within the past 3 months.
- If the patient's BMI is greater than 35, measure the patient's chest circumference at the axillary level. If the chest circumference is >165 cm, sensor implantation should not occur.

1. Frankenstein L, Remppis A, Nelles M, Schaelling B, Schellberg D, Katus H, et al. Relation of N-terminal pro- brain natriuretic peptide levels and their prognostic power in chronic stable heart failure to obesity status. Eur Heart J. 2008;29(21):2634-40.

Warnings

Before use of the system, read and understand the instructions for use contained in this manual and in the System Guide.

- Read this manual thoroughly before using the system to avoid potential patient injury or death.
- Only trained personnel should use this product.
- The implant procedure must be performed by personnel with the appropriate clinical skills and infrastructure to support right heart catheterizations and endovascular device placement and deployment over a guidewire.
- The PA Sensor and Delivery System is for single use only. Do not reuse, reprocess, or resterilize. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.
- The implant procedure must be performed under fluoroscopic guidance.
- Do not use a guidewire with a preformed J-shaped tip for sensor delivery. The preformed J-shaped tip may pull the sensor proximally during guidewire retraction.
- The patient's PA vessel inner diameter must be >7 mm at the site of device implant.
- Following device implantation, all subsequent right heart catheterizations must be performed under fluoroscopic guidance. Without fluoroscopy, there could be inadvertent entanglement between the pulmonary artery catheter and the device.

Precautions

- Only authorized personnel should use this device.
- The delivery system should only be used with a guidewire. Do not aspirate or infuse through the delivery system guidewire lumen during use.
- Follow standard procedure for catheterization of patients receiving anticoagulation therapy. An INR of <1.5 is recommended prior to RHC (Right Heart Catheterization) and implant if patient is on anticoagulant therapy.
- Protect the sensor from surface contamination once removed from the sterile package. Ensure that either talc-less gloves are used for the implantation procedure or rinse all talc from the gloves with sterile saline prior to handling.
- If the hub detaches from the catheter during removal, retract the catheter by holding the shaft.
- Accuracy of the CardioMEMS™ HF System is affected by a change in body temperature (-1 mm Hg/ΔºC).
- Accuracy of the CardioMEMS HF System is slightly affected by large changes in elevation between the initial baseline calibration and subsequent measurements. (+2 mmHg/305 meters elevation change).
- An accurate right heart catheterization is required to set system baseline (mean pressure).
- If a patient has a sensor implanted and another member of the same household is scheduled to have a sensor implanted, contact Technical Support prior to the second patient's implant procedure.
- The mean pressure measurement accuracy of the system may be affected by various factors. Mean pressure measurement error has been observed when the sensor was deployed in a vessel which had an inner diameter of less than 7 mm, and in cases where there was an acute bend in the vessel of >30 degrees at the location of the sensor. Signs of mean pressure measurement error include the following:
  - Gradual mean pressure changes without a corresponding proportional change in the pulse pressure (systolic-diastolic pressure)
  - Negative mean pressures

  If either feature is observed, temporarily suspend use of the pressure information for management of the patient and contact Technical Support for further assistance. A right heart catheterization may be needed to recalibrate the Baseline (mean pressure) in order to continue use of the system.
- Patients who are currently on chronic anticoagulant therapy should restart treatment after sensor implantation. Patients who are not currently being treated with chronic anticoagulant therapy should be placed on aspirin (81 mg or 325 mg) and clopidogrel (75 mg) daily for one month following the procedure. After one month, the patient should continue aspirin therapy.
- Patients with a reduced ejection fraction should be on stable AHA/ACC guidelines based medical therapy prior to implant.
- The PA Sensor is a permanent implant. The sensor does not have any batteries that require replacement or any components that will wear or fail over time. Removal after implantation is not recommended. No circumstances where the sensor needs to be removed have been identified and no sensors were removed during the CHAMPION trial, the CardioMEMS US Post-Approval Study, or the GUIDE HF trial. The sensor should be retrieved by using standard intra-vascular and surgical procedures as would be used for other vascular implants if required.
- If there is evidence of a change in device performance, contact Technical Support for additional information.
- PA Sensor function is unaffected after temporary exposure up to 2 Atmospheres Absolute (ATA) pressure. Follow the contact process under Technical Support for additional information if the patient will have hyperbaric chamber exposure or is planning to scuba dive.
- Pacemakers, ICDs, and Ventricular Assist Devices (VADs) can work in conjunction with the PA Sensor and will

not affect the performance of the system. Several medical procedures can also be performed while the sensor is implanted if precaution is taken to avoid direct contact with the sensor. These procedures include radio-frequency ablation, ionizing radiation, and diagnostic ultrasound. The effects of therapeutic ultrasound have not been determined. If therapeutic ultrasound is required, avoid contact with the sensor.

MRI Information

MR Conditional

Non-clinical testing demonstrated that the sensor is MR Conditional. A patient with this device can be scanned safely immediately after implantation under the following conditions:

- Static magnetic field of 1.5 or 3.0 Tesla
- Maximum spatial gradient magnetic field of 720-Gauss/cm (7200-mT/m) or less

In non-clinical testing, the CardioMEMS™ PA Sensor produced the temperatures in the table below during MRI performed for 15 minutes of scanning (per pulse sequence) in the 1.5-Tesla/64-MHz[1] and 3-Tesla/128-MHz[2] MR systems. These temperature changes will not pose a hazard to the patient under the conditions indicated.

Table 3. MRI Related Heating

	1.5-Tesla	**3-Tesla**
MR system reported whole body averaged SAR	2.9-W/kg	2.9-W/kg
Calorimetry measured values, whole body averaged SAR	2.1-W/kg	2.7-W/kg
Highest temperature change	1.9°C	2.3°C

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the sensor. Selecting optimal MR imaging parameters to compensate for the presence of the sensor may be necessary. The maximum artifact size (as seen on the gradient echo pulse sequence) extends approximately 5 mm relative to the size and shape of the sensor.

Table 4. Artifact Information

Pulse sequence	**T1-SE**	**T1-SE**	**GRE**	**GRE**
Signal void size	305-mm^2	34-mm^2	645-mm^2	101-mm^2
Plane orientation	Parallel	Perpendicular	Parallel	Perpendicular

Explant and Disposal

The sensor does not require removal before cremation. Do not implant an explanted sensor in another patient as sterility, functionality, and reliability cannot be ensured.

Potential Adverse Events

Potential adverse events associated with the implantation procedure include, but are not limited to the following:

- Air embolism
- Allergic reaction due to device component materials or procedure related
- Infection
  - Upper respiratory infection
  - Bronchitis
  - Pneumonia
  - Acute Bronchitis
  - Groin abscess
  - Methicillin-resistant staphylococcal aureus infection
  - Pulmonary Infiltration
  - Sepsis
- Delayed wound healing
- Arrhythmias
  - Ventricular tachycardia
  - Atrial fibrillation
  - Ventricular arrhythmia

1. Magnetom, Siemens Medical Solutions, Malvern, PA. Software Numaris/4, Version Syngo MR 2002B DHHS Active-shielded, horizontal field scanner
2. Excite, HDx, Software 14X.M5, General Electric Healthcare, Milwaukee, WI

    - Ventricular fibrillation
    - Atrial fibrillation with rapid ventricular response
    - Atrial flutter
    - Cardiac dysrhythmias
    - Tachycardia
    - Wide complex tachycardia
    - Atrial dysrhythmia
- Bleeding
    - Epistaxis/Nose bleeds
    - GI bleed
    - Bleeding – Other
    - Blood in stool
    - Catheter site bleeding
    - Catheter site ecchymosis
    - Hematuria
- Hemoptysis
- Hematoma (Bruising)
- Hematoma
    - Catheter site hematoma
    - Vessel puncture site hematoma
- Nausea
- Cerebrovascular accident
    - Stroke/Transient ischemic attack
- Thrombus
    - Arterial thrombosis (limbs)
    - Blood clot
- Cardiovascular Injury
    - Valve damage
    - Pseudoaneurysm formation
    - AV Fistula
    - Pulmonary artery injury
- Myocardial infarction (Heart attack)
- Death
- Embolism
    - Pulmonary infarct
    - Pulmonary embolism
    - Device embolization
- Thermal Burn
- Cardiac Perforation
- Pneumothorax, thoracic duct injury, or hemothorax

Instructions for Use

Personnel Training

Implanting physicians are required to have successfully completed additional training in the use of the PA Sensor and Delivery System prior to implant.

Accessories

The accessories required to implant the device and set the sensor's PA pressure baseline are listed in the following table. These accessories are not packaged with the device.

Table 5. Accessories

Item	Specifications
Vascular Access Kit	12 Fr Introducer sheath and dilators with access guidewire
PA Catheter	110 cm length

Sensor Delivery Guidewire	0.018” x 260-300 cm fixed core guidewire with straight or angled tip (no J-tip)

In addition to the specified accessories, the following catheter lab equipment and supplies are required to implant and set the sensor’s PA pressure baseline:

- Fluoroscope with digital angiography capabilities and ability to record and recall images (C-arm or fixed)
- Blood pressure monitoring equipment for a right heart catheterization procedure
- Saline solution
- Radiopaque contrast media

Package Inspection

Inspect the package carefully before opening and check the Use By date on the product label. Implant of the sensor is not recommended after its expiration date. If the integrity of the sterile package has been compromised, or the product or package is defective, do not use the product and contact Technical Support.

Package Contents

The sensor is packaged separately and supplied sterile. Packages contain:

- 1 PA Sensor and Delivery System
- 1 USB flash drive
- 1 temporary patient implant card
- Product documentation

Sterilization

The package contents have been sterilized with ethylene oxide before shipment. The system is for single use and is not intended to be resterilized. If the sterile package has been compromised, contact Technical Support.

Pre- and Post-Procedure Antiplatelet Regimen

Patients who are currently on anticoagulant therapy, or those in which chronic anticoagulant therapy is indicated for heart failure treatment, will restart treatment after sensor implantation. An INR of <1.5 is recommended prior to sensor implant for patients who were previously on anticoagulant therapy. Patients should discontinue use of anticoagulant therapy 1-2 days prior to sensor placement. The standard of care as bridge therapy to sensor placement should be used in patients who were on anticoagulant therapy.

Patients who are not being treated with chronic anticoagulant therapy should be placed on aspirin (81 mg or 325 mg) and clopidogrel (75 mg) daily for one month following sensor placement. After one month, the patient should continue with aspirin therapy only. It is important to resume or initiate antiplatelet or anticoagulant therapy following sensor implantation to reduce the likelihood of thrombotic events.

For patients at risk for gastrointestinal bleeding during the period in which dual antiplatelet therapy is given, the physician should consider a proton pump inhibitor. Patients at risk include the elderly or those with a history of gastroduodenal ulcers, GERD, esophagitis, intestinal polyps or cancer. Patients who smoke or who are using steroids or non-steroidal anti-inflammatory drugs may also be at risk.

Implantation Procedure

Hospital Electronics System Setup

To set up the Hospital Electronics System:

- Mount the external system on an IV pole.
- Position the IV pole near the head of the patient and on the same side as the implant site.
- Plug the power cord into a wall outlet.
- Insert the USB flash drive that came with the PA Sensor and Deliver System.
- Turn on the power to the system.
- Select New Implant.
- Either select or enter the patient information.
- Confirm that the sensor serial number displayed on the screen matches the number on the sensor product.
- Place the right and left ECG electrodes high on the shoulders and place the reference electrode below the chest. The leads should be routed away from the chest. ECG leads draped near the antenna or antenna cable can reduce sensor signal strength.

Right Heart Catheterization and Sensor Implant Procedure

- Gain percutaneous access to the left or right femoral vein or internal jugular vein.
- Introduce 12 Fr introducer sheath over a 0.035 mm guidewire.
- Remove the dilator and guidewire.

- Insert and advance the pulmonary artery (PA) catheter, with balloon inflated, until it reaches a wedge position in the lower lobe region of the left or right pulmonary artery.
- Measure PA and PA wedge pressure.
- Measure cardiac output (optional).
- Identify target implant site by angiogram through the PA catheter distal lumen (5 cc hand injection of radiographic contrast) with the balloon inflated. Care should be taken to verify balloon location and lack of over-wedging prior to contrast injection.

Target implant site criteria:

- Target implant vessel is within the lower lobe of either lung and the vessel is directed towards the feet and back.
- Vessel diameter is >7 mm and has <30 degree angulation where body of Sensor will be placed.
- Vessel diameter is 5–8 mm where the distal loop of Sensor will be placed. See the figure below.

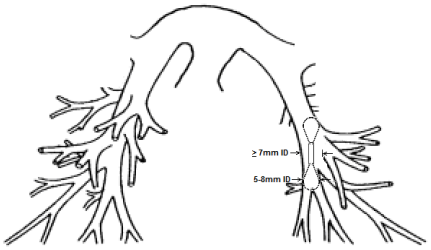


Figure 3. Target implant site

- Insert the sensor delivery guidewire through the PA catheter, across the target implant site.
- Retract and remove the PA catheter while maintaining the guidewire position.
- Remove the sensor from the package and flush the guidewire lumen with saline.
- Carefully swirl the distal end of the catheter (at least 20 cm from the tip) in a bowl of saline to activate the hydrophilic coating.
- Introduce the sensor delivery catheter over the guidewire through the sheath and into the deployment position at the target implant site.
- Release the sensor: Unscrew the cap on the delivery catheter hub, then retract and remove the wires from the catheter.
- Under fluoroscopic monitoring, slowly and gently retract and remove the delivery catheter while maintaining guidewire and sensor position. If resistance is encountered, do not forcibly retract the hub or catheter shaft.
- Insert the PA catheter over the guidewire into the main PA.
- Slowly remove the guidewire while maintaining sensor position.
- Position the PA catheter tip approximately 5-10 cm proximal to the sensor or within the opposite lung and measure PA pressure.
- Acquire the sensor signal using the Hospital Electronics System antenna placed under the patient's back, centered under the sensor position.
- Set Mean PA Pressure Baseline: Once a valid PA pressure waveform is observed on both the PA catheter and Hospital Electronics System displays, press the Set Pressure Baseline button on the Hospital Electronics System. Enter the mean PA pressure value measured by the PA catheter.
- Set Cardiac Output Baseline: Press the Set CO Baseline button on the Hospital Electronics System. Enter the Cardiac Output value which was measured by the PA catheter. (Optional)
- Press the Take Reading button to capture baseline reading(s).
- Remove antenna from under patient's back.
- Remove pulmonary artery catheter and introducer sheath.
- Close venous access site per standard of care.

Patient Identification Card

A temporary patient identification card is provided in the device packaging and should be given to the patient after implantation. Advise patients to keep this card in their possession at all times. A permanent card will be mailed to the patient within a few weeks after discharge.

Patient Counseling Information

Discuss these topics with patients prior to discharge:

- Signs and symptoms of infection
- Reporting symptoms
- EMI and RF Interference

Clinical Study Information

Introduction

Heart failure (HF) is a life-threatening condition with debilitating symptoms and is a burden to patients and their caregivers. Over 60 million people are estimated to be living with heart failure worldwide. It has been shown that pulmonary artery (PA) pressures begin to increase earlier than signs and symptoms of worsening heart failure (for example, weight gain or shortness of breath) and can provide a physiologic basis for heart failure patient management.

The CardioMEMS™ HF System provides a proven method for measuring PA pressure using a wireless pressure sensor implanted into the pulmonary artery. The CardioMEMS HF System provides clinicians with a patient's PA pressure while the patient is at home, without the need for a procedure or an office visit. This information allows the physician to manage the patient's heart failure proactively with the goal of controlling PA pressures and reducing heart failure hospitalizations.

GUIDE HF Trial – Randomized Arm

The applicant performed a clinical study in the US under IDE#G170258 to establish a reasonable assurance of safety and effectiveness of the CardioMEMS HF System to guide the treatment of patients with New York Heart Association (NYHA) Class II – IV heart failure. Data from this clinical study were the basis for the current PMA supplement approval decision. A summary of the clinical study is presented below.

Study Design

Patients were enrolled from 3/15/2018 to 12/20/2019. The database for the Panel Track Supplement reflected data collected through Jan 18, 2021 and included 1007 patients from 114 U.S. sites and 15 patients at 4 sites in Canada.

The study was a prospective, randomized, controlled, single-blind, multi-center, pivotal clinical trial. The study enrolled subjects with NYHA Class II, III, or IV heart failure and either elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] or B-type natriuretic peptide [BNP]) and/or a prior HF hospitalization. All enrolled subjects underwent a right heart catheterization and implantation of a CardioMEMS device. Successfully implanted subjects were then randomized 1:1 to either hemodynamic-guided management using information provided by the CardioMEMS HF System (Treatment group) or heart failure management according to the standard of care (Control group). All patients took daily readings from home, but they were blinded to the treatment assignment or PA pressure measurements. Clinicians had access to pulmonary artery pressure information for patients in the Treatment group but not for patients in the Control group. Patient contacts were performed with scripted calls and equalized between two groups.

The study was evaluated for success based on the composite of HF hospitalization, urgent HF visits (emergency department or hospital outpatient visits for intravenous diuretic therapy), and all-cause mortality at 12 months. The study would be considered successful by demonstrating that the hemodynamic-guided HF treatment is superior to the control therapy for heart failure outcomes.

An independent Clinical Events Committee (CEC) provided blinded adjudication for all primary endpoint events. An independent Data Safety Monitoring Board (DSMB) oversaw clinical data and safety.

Clinical Inclusion and Exclusion Criteria

Enrollment in the GUIDE-HF Trial (Randomized Arm) was limited to patients who met the following inclusion criteria:

1. Diagnosis and treatment for HF (regardless of LVEF) for >90 days prior to the date of consent. Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current AHA/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, with any intolerance documented.
2. NYHA Class II, III or IV HF symptoms documented within 30 days prior to consent.
3. HFH within 12 months prior to consent and/or elevated NT-proBNP (or BNP) within 30 days prior to consent defined as:
    a. Subjects with LVEF ≤40%: NT-proBNP ≥1000 pg/ml (or BNP ≥250 pg/ml).
    b. Subjects with LVEF >40%: NT-proBNP ≥700 pg/ml (or BNP ≥175 pg/mL).
    c. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF >40%) will be corrected for BMI using a 4% reduction per BMI unit over 25 kg/m².[1]
4. ≥18 years of age
5. Chest circumference of <65 inches, if BMI is >35 kg/m²
6. Written informed consent obtained from subject

1. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF >40%) were corrected for BMI using a 4% reduction per BMI unit over 25 kg/m² per the Frankenstein equation.

7. Willing and able to upload PA pressure information and comply with the follow-up requirements

Patients were not permitted to enroll in the GUIDE-HF Trial (Randomized Arm) if they met any of the following exclusion criteria:

1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNi), and beta-blockers)
2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
3. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 12 months
4. NYHA Class IV HF patients with:
    a. Continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of ≤4, OR
    b. Persistence of fluid overload with maximum (or dose equivalent) diuretic intervention
5. Glomerular Filtration Rate (eGFR) <25 ml/min and non-responsive to diuretic therapy, or receiving chronic dialysis
6. Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for one month post-implantation
7. Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS™ PA Sensor
8. Implanted with mechanical right heart valve(s)
9. Unrepaired severe valvular disease
10. Pregnant or planning to become pregnant in the next 12 months
11. An active, ongoing infection, defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum or urine).
12. History of current or recurrent (≥ 2 episodes) pulmonary emboli and/or deep vein thromboses
13. Major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent
14. Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent
15. Enrollment into another trial with an active treatment arm
16. Anticipated life expectancy of <12 months
17. Any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (e.g., trans-pulmonary gradient >15) at implant RHC, a history of non-compliance, or any condition that would preclude CardioMEMS PA Sensor implantation.

Follow-up Schedule

All randomized patients were scheduled to return for follow-up examinations at 6 and 12 months. Adverse events and complications were recorded at all visits.

The key time points are shown in Table 6 summarizing schedule of treatments and evaluations.

Table 6. Schedule of Treatments and Evaluations

Visit Trial Activity	Baseline (up to – 60 days)	Implant (time zero)	Prior to Discharge	Phone Contact[1] (Randomized Arm Only)	6 months (+/-14 days)	12 months (+/-30 days)
Informed Consent Process	X					
Assessment of Inclusion/ Exclusion Criteria	X					
Demographic Information	X					
Cardiovascular History	X					
BMI (and Chest Circumference if BMI >35kg/m^2)	X					
Limited Echo for EF (if no EF documented)	(X)					
EQ-5D-5L and KCCQ-12 Administration	X				X	X
Creatinine and Calculation of eGFR	X				X	X
NT-proBNP (or BNP)	X				X	X
Medication Review and Documentation	X		X		X	X
HF Exam (Including NYHA Assessment)	X				X	X
6MHW Test	X				X	X
CardioMEMS™ HF System Information		X				
Catheterization Laboratory PA Pressure Measurements		X				
Randomization (Randomized Arm Only[2])			X			
Subject Teaching / Compliance Assessment			X	X	X	X
Subject Contact Worksheet				X		
Medication Update Documentation		(X)	(X)	(X)	(X)	(X)
Reportable AEs	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Non-AE Device Issues		(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

(X) If applicable/as it occurs

1. All sites will be required to be in contact with each subject in the Randomized Arm (including subjects in the Treatment and Control Groups) at least once every two weeks during the first three months from the date of implantation and then at least once per month from three months to the 12 month follow-up visit.
2. Randomization should be completed as soon as possible but within 24 hours of implant, and prior to discharge.

Clinical Endpoints

With regards to effectiveness, the primary endpoint is a composite of the following:

- Hospitalization (≥ 24 hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy
- An unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit,

or hospital inpatient visit and intravenous administration of diuretic therapy

- All-cause mortality

With regards to safety, the secondary safety endpoint is freedom from Device or System Related Complications (DSRCs) at 12 months post-implantation.

DSRC was defined as an adverse event that was related to or possibly related to the system (wireless pressure sensor or external electronics) and had at least one of the following characteristics:

- Treated with invasive means (other than intramuscular medication or an RHC used for diagnostic purposes)
- Resulted in the death of the subject
- Resulted in the explant of the device

With regard to success/failure criteria, study success was defined as demonstrating superiority for the primary endpoint hypotheses below at a significance level of 2.5%:

H0: Hazard ratio (HR) for the Composite Endpoint at 12 months (Treatment to Control) ≥ 1

H1: HR for the Composite Endpoint at 12 months (Treatment to Control) <1

or

H0: $e^{\beta 1} \geq 1$

H1: $e^{\beta 1} < 1$

where e is the exponential function and β1 is the regression coefficient obtained from the covariate representing randomized group (Treatment or Control) in the Andersen-Gill model. Thus, the hazard ratio is the exponentiation of the regression coefficient for randomized group. This is equivalent to testing the regression coefficient against zero.

All randomized subjects were included in the analysis population.

Accountability of PMA Cohort

A total of 1022 patients were consented for trial enrollment and underwent a right heart catheterization and attempted implantation of a CardioMEMS™ device. Of these, 22 did not receive an implant, primarily due to anatomical/physiological conditions identified during the right heart catheterization. The observed PA sensor implant success rate was 97.8%. The remaining 1000 subjects who received a successful implant were randomized 1:1 to either the Treatment group (N = 497) or the Control group (N = 503). At the time of database lock, 854 (85.4%) randomized subjects completed the 12-month follow-up visit. Figure 4 summarizes the subject disposition in the PMA study.

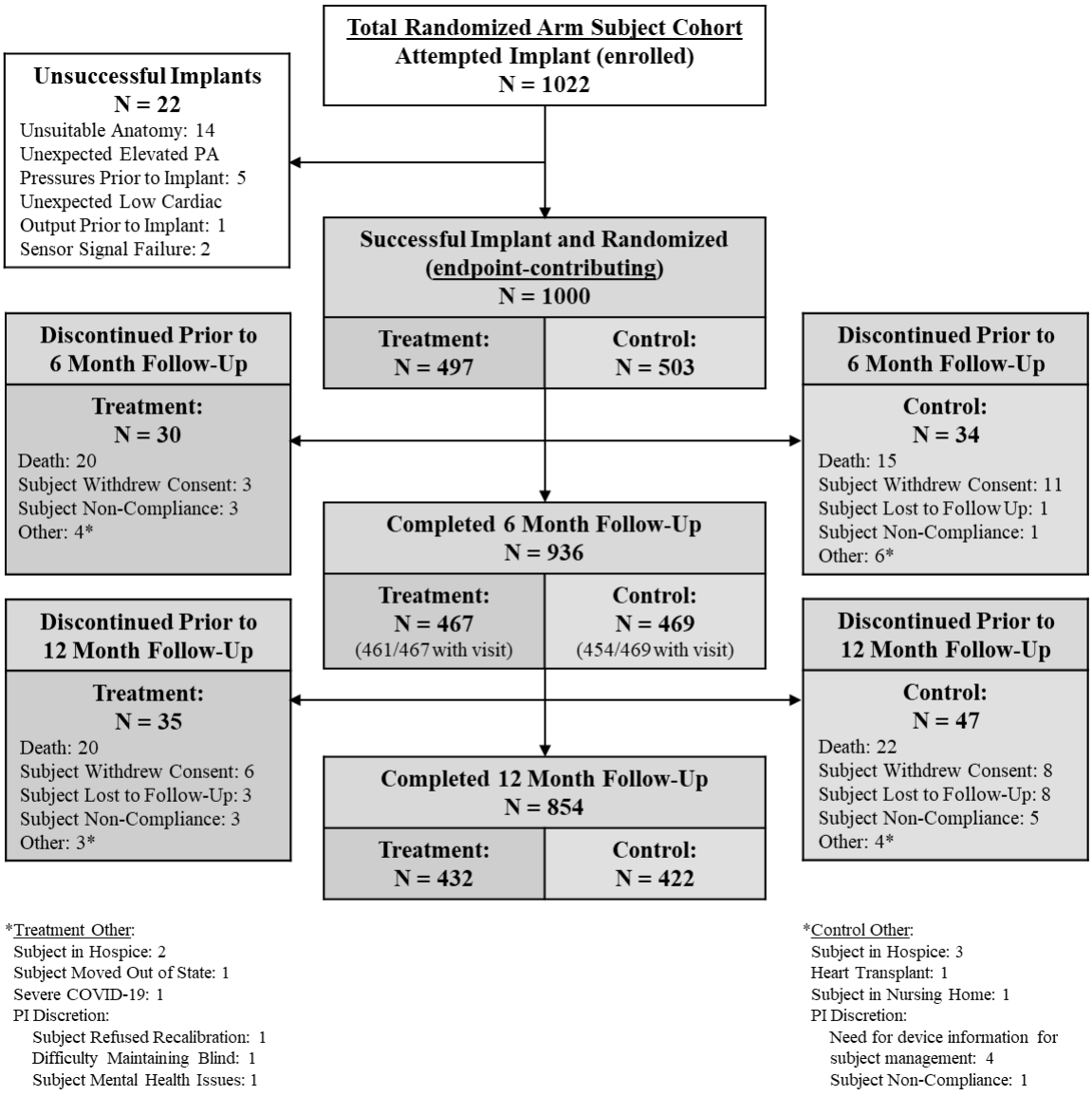


Figure 4. Subject Disposition

The protocol specified the following analysis populations:

Endpoint Analysis Population: All randomized subjects (N = 1000)

Safety Population: All enrolled subjects (N = 1022)

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a heart failure study that enrolls NYHA Class II-IV patients in the US. The mean age was 69.2 ± 11 years and 37.5% were female. NYHA II, III, and IV patients account for 29.6%, 65.0%, and 5.4% of the randomized subjects. Table 7 presents the demographics and patient characteristics by randomized group. The Treatment and Control groups were balanced in all relevant demographics and baseline characteristics.

Table 7. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N=497)	Control (N=503)	p-value[1]
Age – year	69.2 ± 11.1 (497)	69.2 ± 11.0 (503)	0.8996
Female Sex	37.6% (187/497)	37.4% (188/503)	0.9480
Race			
White	81.1% (403/497)	80.5% (405/503)	0.8725
Black	17.5% (87/497)	18.5% (93/503)	0.7420
Asian	0.0% (0/497)	0.2% (1/503)	1.0000
American Indian or Alaskan Native	0.4% (2/497)	0.4% (2/503)	1.0000
Pacific Islanders	0.0% (0/497)	0.0% (0/503)	
Other	1.2% (6/497)	0.6% (3/503)	0.3389
Ethnicity			
Hispanic	3.2% (16/497)	3.4% (17/503)	1.0000
Non-Hispanic	96.0% (477/497)	96.0% (483/503)	1.0000
Unknown	0.8% (4/497)	0.6% (3/503)	0.7241
Body mass index – kg/m^2	32.9 ± 8.3 (497)	33.8 ± 8.4 (503)	0.0571
NYHA Class			
II	29.4% (146/497)	29.8% (150/503)	0.8900
III	64.8% (322/497)	65.2% (328/503)	0.8947
IV	5.8% (29/497)	5.0% (25/503)	0.5778
Medical History			
Ischemic etiology	41.6% (207/497)	37.8% (190/503)	0.2198
Previous myocardial infarction	29.0% (144/497)	31.4% (158/503)	0.4093
Previous percutaneous coronary intervention	33.2% (165/497)	31.4% (158/503)	0.5885
Previous coronary artery bypass grafting	27.2% (135/497)	27.0% (136/503)	1.0000
Diabetes	48.9% (243/497)	51.9% (261/503)	0.3759
Cerebrovascular accident	13.3% (66/497)	12.9% (65/503)	0.9254
Atrial flutter or fibrillation	60.4% (300/497)	57.9% (291/503)	0.4404
Vital Signs and Hemodynamic Analyses			
Heart rate – bpm	73.8 ± 12.5 (497)	74.2 ± 12.3 (503)	0.7438
Systolic blood pressure – mmHg	121.6 ± 19.1 (497)	120.8 ± 18.1 (503)	0.6134
Diastolic blood pressure – mmHg	69.2 ± 10.8 (497)	69.0 ± 10.8 (503)	0.7996
Left ventricular ejection fraction – %	39.4 ± 17.3 (497)	40.7 ± 16.9 (503)	0.1870
Left ventricular ejection fraction >40%	45.1% (224/497)	48.7% (245/503)	0.2546
Pulmonary artery systolic pressure –mmHg	44.9 ± 13.9 (497)	45.2 ± 14.6 (503)	0.9194
Pulmonary artery diastolic pressure –mmHg	18.9 ± 8.0 (497)	18.8 ± 7.7 (503)	0.8203
Pulmonary artery mean pressure –mmHg	29.2 ± 9.5 (497)	29.4 ± 10.0 (503)	0.9631
Pulmonary capillary wedge pressure –mmHg	17.3 ± 8.0 (495)	17.6 ± 7.9 (503)	0.6171
Cardiac output – L/min	4.83 ± 2.62 (497)	4.70 ± 1.46 (503)	0.8459
Cardiac index – L/min/m^2	2.27 ± 1.11 (497)	2.19 ± 0.63 (503)	0.4609

Table 7. Subject Demographics and Characteristics (Endpoint Analysis Population)

	Treatment (N=497)	Control (N=503)	p-value[1]
Ambulatory Hemodynamics during First Week			
Pulmonary artery systolic pressure –mmHg	46.3 ± 14.4 (497)	46.2 ± 13.3 (499)	0.7640
Pulmonary artery diastolic pressure –mmHg	22.4 ± 7.8 (497)	22.7 ± 7.4 (499)	0.4141
Pulmonary artery mean pressure –mmHg	31.8 ± 10.2 (497)	31.9 ± 9.6 (499)	0.6693
Heart rate – bpm	78.8 ± 11.7 (497)	79.4 ± 11.9 (499)	0.7893
Laboratory Analyses			
Serum creatinine level – µmol/L	128.5 ± 44.5 (495)	133.5 ± 48.5 (495)	0.1548
Estimated glomerular filtration rate – ml/min/1.73m^2	54.3 ± 21.3 (495)	52.8 ± 20.8 (494)	0.2469
B-type natriuretic peptide level – pg/m	520.7 ± 689.2 (261)	552.4 ± 954.0 (256)	0.8499
N-terminal pro-B-type natriuretic peptide level – pg/mL	2460 ± 3707 (219)	2183 ± 2803 (225)	0.5287
Treatment History			
Previous cardiac resynchronization therapy	28.6% (142/497)	32.4% (163/503)	0.1926
Previous implantation of defibrillator	42.9% (213/497)	40.8% (205/503)	0.5217
Guideline-Directed Medical Therapy			
ACE-Inhibitor or ARB or ARNi	64.2% (319/497)	63.6% (320/503)	0.8953
ARNi	29.2% (145/497)	27.6% (139/503)	0.6236
Beta Blocker	89.3% (444/497)	87.9% (442/503)	0.4873
Mineralocorticoid Receptor Antagonist	47.7% (237/497)	42.9% (216/503)	0.1440
Diuretic	95.4% (474/497)	95.0% (478/503)	0.8827
Hydralazine	16.3% (81/497)	15.9% (80/503)	0.9315
Nitrate	19.9% (99/497)	20.5% (103/503)	0.8749
SGLT2 Inhibitor	1.3% (2/152)	1.4% (2/140)	1.0000
Enrollment Type			
Heart failure hospitalization in year prior only	34.2% (170/497)	38.0% (191/502)	0.2114
Elevated natriuretic peptide level in 30 day prior only	46.3% (230/497)	42.2% (212/502)	0.2032
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.5% (97/497)	19.7% (99/502)	0.9367
KCCQ-12 at Baseline – Overall Summary Score	54.9 ± 24.3 (494)	54.9 ± 23.8 (497)	0.8876
6MHW at Baseline – m	235.2 ± 120.2 (474)	229.6 ± 123.0 (482)	0.4459

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

1. Continuous variables compared using Wilcoxon Rank Sum test, and categorical variables compared using Fisher's exact test.

Safety and Effectiveness Results

Effectiveness Results

Primary Endpoint

The primary endpoint analysis was based on all randomized subjects. At 12 months, there were 253 primary endpoint events in the Treatment group compared with 289 events in the Control group. The difference between the groups represented a non-significant 12% relative risk reduction in the primary endpoint events (0.563 vs. 0.640 events per patient-year; HR 0.88, 95% CI 0.74-1.05, p=0.1624). Since the 97.5% upper confidence bound of the hazard ratio was not less than 1, the primary endpoint was not met.

The table below presents the primary endpoint analysis and the components. There were 185 heart failure hospitalizations in the treatment group and 225 in the control group (0.410 vs. 0.497 events per patient; HR 0.83, 95% CI 0.68-1.01). The rates of urgent heart failure ED/outpatient visits or mortality were similar between the two groups.

The timing of the pivotal study overlapped with the COVID-19 pandemic. The effects of the pandemic on the study outcomes are further assessed in the sensitivity analysis section below.

Table 8. Primary Endpoint Analysis and Components

Endpoint[1]	**Treatment (N=497) Events (Rate**[2]**)**	**Control (N=503) Events (Rate**[2]**)**	**Hazard Ratio (95% CI) p-value**[3]
HF Hospitalization + ED/ OP + Death (Primary Endpoint)	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05), p=0.1624
HF Hospitalization + ED/OP (Secondary Endpoint)	213 (0.474)	252 (0.557)	0.85 (0.70, 1.03), p=0.0958
HF Hospitalization	185 (0.410)	225 (0.497)	0.83 (0.68, 1.01)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	28 (0.065)	27 (0.063)	1.04 (0.61, 1.77)
Death	40 (0.094)	37 (0.086)	1.09 (0.70, 1.70)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
2. Event Rate is an annualized rate estimated from the Andersen-Gill model.
3. Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich variance estimates.

COVID-19 Impact Sensitivity Analysis

COVID-19 Sensitivity Analysis for Interaction

The COVID-19 pandemic occurred while the pivotal study was still ongoing. Across North America, hospitals saw notable reduction in heart failure hospital admissions during COVID-19 lockdowns. Using the national emergency declaration date (March 13, 2020) in the United States as the onset date, a total of 71.7% of follow-up had been completed prior to COVID-19. The median follow-up prior to COVID-19 was 8.4 months.

The applicant added a COVID-19 impact sensitivity analysis (dated July 7, 2020) to the statistical analysis plan prior to data unblinding. The sensitivity analysis would descriptively compare the primary endpoint event rates observed during subject follow-up occurring prior to the start of the COVID-19 pandemic to rates observed during subject follow-up occurring after the start of the pandemic to evaluate impact of COVID-19, as shown in Figure 5.

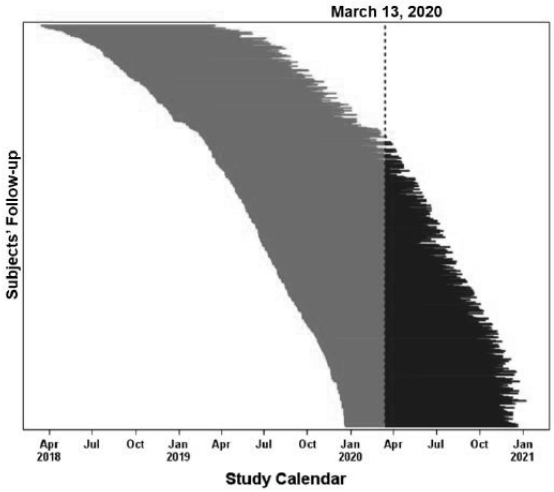


Figure 5. COVID-19 Impact Sensitivity Analysis

The sensitivity analysis demonstrated a qualitative interaction with a significant p-value of p=0.1129 (<p=0.15, pre-specified interaction p-value threshold), suggesting an impact of COVID-19 on the treatment effect observed in the Randomization Arm of the GUIDE-HF trial (Table 9). The hazard ratio for the primary endpoint events reversed from 0.81 prior to COVID-19 to 1.11 during COVID-19.

Table 9. Primary Endpoint – COVID-19 Impact Sensitivity Analysis

Endpoint[1]	Treatment (N=497) Events	Control (N=503) Events	Forest Plot	Hazard Ratio (95% CI)[2]
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)				**Interaction p-value[3]** p=0.1129
Prior to COVID-19[4]	177	224		0.81 (0.66, 1.00)
During COVID-19[4]	76	65	0.5 0.75 1 1.25 1.5 1.75	1.11 (0.80, 1.55)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
2. Contrast Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich estimates.
3.Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.
4.Primary Endpoint events are analyzed through March 13, 2020 for Prior to COVID-19 and analyzed after March 13, 2020 for During COVID-19.

Since the COVID-19 sensitivity analysis suggested an effect of COVID-19 on the primary endpoint, the pre-pandemic data were further explored.

Pre-COVID-19 Analysis

Pre-pandemic Primary Endpoint Events

- Prior to COVID-19, there were a total of 177 primary endpoint events in the Treatment group compared with 224 events in the Control group (0.595 events vs. 0.730 events per patient, respectively). An HR of 0.81 (95% CI 0.66-1.00) for the primary endpoint, largely driven by a 27% reduction in risk for HFH, was observed.

The results of the analysis including data prior to COVID-19 only are shown in the table below:

Table 10. Primary Endpoint and Components – Including Data Prior to COVID-19 Only

Endpoint[1]	**Treatment (N=497) Events (Rate[2])**	**Control (N=503) Events (Rate[2])**	**Hazard Ratio (95% CI)[3]**
HF Hospitalization + ED/OP + Death (Primary Endpoint)	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)
HF Hospitalization + ED/OP (Secondary Endpoint)	147 (0.502)	199 (0.660)	0.76 (0.61, 0.95)
HF Hospitalization	124 (0.426)	176 (0.587)	0.73 (0.57, 0.92)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	23 (0.077)	23 (0.076)	1.02 (0.57, 1.82)
Death	30 (0.103)	25 (0.083)	1.24 (0.73, 2.10)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date. Primary Endpoint events are analyzed through March 13, 2020.
2. Event Rate is an annualized rate estimated from the Andersen-Gill model.
3. Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.

Quality of Life Assessment and Functional Assessment (6MHW)

Health status changes over time were assessed by EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire and Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at baseline, 6, and 12 months. While both Treatment and Control groups gained improvement at 6 months, there were no significant differences between the groups (Table 11).

The functional assessment of 6MHW distance did not show a significant improvement either within or between groups over the follow-up period.

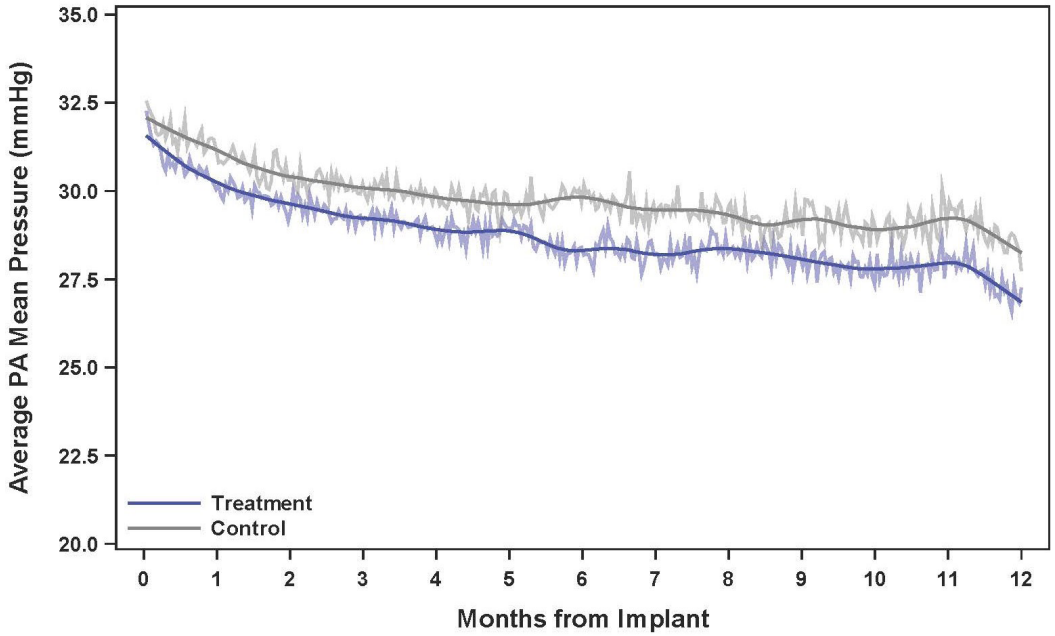
Table 11. KCCQ-12, EQ-5D-5L, and 6MHW

	6 Month Paired Change from Baseline			**12 Month Paired Change from Baseline**		
Component/ Analysis	**Treatment** Mean ± SD (n)	**Control** Mean ± SD (n)	Between Group p-value	**Treatment** Mean ± SD (n)	**Control** Mean ± SD (n)	Between Group p-value
KCCQ-12 Overall	7.44 ± 20.68 (449)	6.14 ± 24.72 (440)	0.3545[1]	5.20 ± 21.35 (421)	4.12 ± 22.50 (408)	0.4783[1]
Summary Score EQ-5D-5L Visual	3.09 ± 19.40 (449)	3.20 ± 21.69 (441)	0.9363[1]	0.94 ± 20,17 (421)	2.90 ± 20.71 (409)	0.1658[1]
Analogue Scale 6MHW Test Distance	0.01 ± 87.78 (332)	2.29 ± 93.69 (342)	0.7439[1]	-12.83 ± 100.08 (288)	-6.46 ± 106.57 (291)	0.4586[1]

1. Student-test comparing Treatment vs. Control change from baseline at 6 months and 12 months

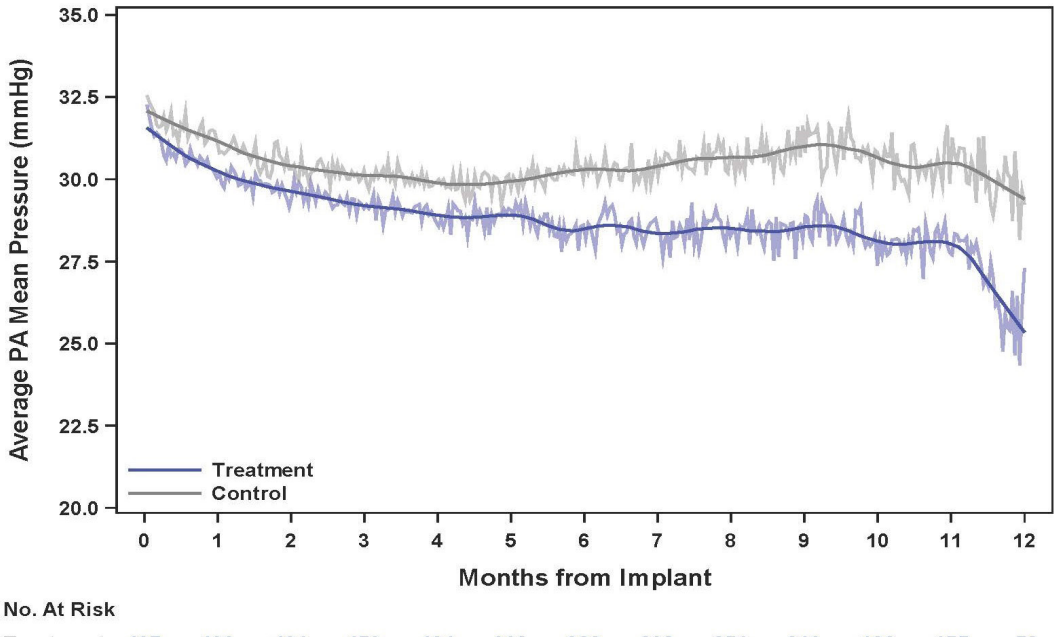
PA Pressures

A reduction in PA mean pressure over time was observed in the Treatment group compared to Control (-2.4 ± 5.2 mmHg vs. -1.7 ± 5.0 mmHg; Figure 6). A greater reduction in Treatment group PA mean pressure was also observed when limited to data prior to COVID-19 (-2.1 ± 4.8 mmHg vs. -1.4 ± 4.8 mmHg; Figure 7).



No. At Risk													
Treatment	497	496	491	486	480	473	468	465	456	447	441	422	193
Control	503	500	494	488	482	476	468	463	459	456	442	434	180

Figure 6. Average PA Mean Pressure Over Time



No. At Risk													
Treatment	497	496	491	459	404	360	328	290	251	216	182	155	58
Control	503	500	494	459	405	365	335	303	272	237	200	172	59

Figure 7. Average PA Mean Pressure Over Time – Data Prior to COVID-19 Only

Safety Results

Freedom from Device or System Related Complications (DSRC)

A total of 8 DSRC events occurred in 8 subjects in the safety population. The observed rate of freedom from Device or System Related Complications was 99.2% (1014/1022). None of the 8 DSRCs resulted in death or explant of the device, and most were vascular injury events due to vascular access or device implant. Table 12 presents a summary of DSRCs.

Table 12. Summary of DSRCs as Adjudicated by the CEC (Safety Population)

Cohort System Organ Class Preferred Term	Number of DSRCs	Proportion of Subjects with DSRCs	Treated with Invasive Means	DSRC Criteria Met	
				Resulted in Death	Resulted in Device Explant
Safety Population (N=1022)					
General Disorders and Administration Site Conditions	**5**	**0.49% (5/1022)**	**5**	**0**	**0**
Catheter Site Hematoma	1	0.10% (1/1022)	1	0	0
Catheter Site Hemorrhage	2	0.20% (2/1022)	2	0	0
Device Dislocation	1	0.10% (1/1022)	1	0	0
Device Malfunction	1	0.10% (1/1022)	1	0	0
Injury, Poisoning and Procedural Complications	**3**	**0.29% (3/1022)**	**3**	**0**	**0**
Arterial Injury	2	0.20% (2/1022)	2	0	0
Vascular Pseudoaneurysm	1	0.10% (1/1022)	1	0	0
Total	**8**	**0.78% (8/1022)**	**8**	**0**	**0**

Hospitalizations

Table 13 summarizes the all-cause hospitalizations reported during the 12-month follow-up for all randomized subjects. Treatment group experienced a lower all-cause hospitalizations rate comparing to the Control group (468 vs. 492) though similar proportion of subjects in each group had at least one hospitalization during the study.

Table 13. Summary of Hospitalizations as Adjudicated by the CEC (Endpoint Analysis Population)

	Treatment (N=497)		Control (N=503)	
Adjudicated Cause	**Count [Rate[1]]**	**Percent of Subjects with Event**	**Count [Rate[1]]**	**Percent of Subjects with Event**
Worsening heart failure	**233 [50.3]**	**27.4% (136/497)**	**269 [57.7]**	**30.4% (153/503)**
HF Hospitalization	185 [39.9]	24.1% (120/497)	225 [48.2]	27.6% (139/503)
Urgent HF Visit	28 [6.04]	4.4% (22/497)	27 [5.79]	5.0% (25/503)
Not a Protocol Defined HF Admission	20 [4.32]	3.4% (17/497)	17 [3.65]	3.0% (15/503)
Other cardiovascular	**200 [43.2]**	**27.4% (136/497)**	**186 [39.9]**	**25.0% (126/503)**
CABG	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Myocardial Infarction or Other Forms of Ischemic Heart Disease	26 [5.61]	4.0% (20/497)	46 [9.86]	7.6% (38/503)
Product Issue[2]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Thrombosis or Thromboembolism	12 [2.59]	2.0% (10/497)	6 [1.29]	1.2% (6/503)
Valve Surgery	5 [1.08]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
Ventricular or Atrial Arrhythmia	57 [12.3]	9.1% (45/497)	55 [11.8]	8.5% (43/503)
Other	99 [21.4]	14.7% (73/497)	72 [15.4]	11.9% (60/503)
Non-cardiovascular	**35 [7.55]**	**6.8% (34/497)**	**37 [7.93]**	**6.4% (32/503)**
Total	**468 [101.0]**	**47.1% (234/497)**	**492 [105.5]**	**46.5% (234/503)**

1. Rate is number of events per 100 subject years.
2. Hospitalization due to events related to the device.

Mortality

A total of 77 subjects died in the study. There were 40 (0.094) all-cause deaths in the Treatment group and 37 (0.086) all-cause deaths in the Control group. Table 14 presents the causes of deaths between the two groups per CEC adjudication.

Table 14. Summary of Deaths as Adjudicated by the CEC (Endpoint Analysis Population)

Adjudicated Cause	Treatment (N=497)	Control (N=503)
Cardiovascular	**6.0% (30/497)**	**4.8% (24/503)**
Cardiovascular procedure	0.2% (1/497)	0.0% (0/503)
Heart failure	3.4% (17/497)	3.0% (15/503)
Sudden cardiac death	2.2% (11/497)	1.8% (9/503)
Other	0.2% (1/497)	0.0% (0/503)
Non-cardiovascular	**1.6% (8/497)**	**2.6% (13/503)**
Gastrointestinal	0.0% (0/497)	0.2% (1/503)
Hemorrhage	0.0% (0/497)	0.2% (1/503)
Infection	0.6% (3/497)	0.6% (3/503)
Inflammatory, Immune (including autoimmune)	0.0% (0/497)	0.2% (1/503)
Neurological	0.2% (1/497)	0.2% (1/503)
Pulmonary	0.2% (1/497)	0.4% (2/503)
Renal	0.4% (2/497)	0.4% (2/503)
Other non-cardiovascular	0.2% (1/497)	0.4% (2/503)
Undetermined cause of death	**0.4% (2/497)**	**0.0% (0/503)**
Total	**8.0% (40/497)**	**7.4% (37/503)**

There were no device-related deaths.

Two subjects died within 30 days after the procedure. A patient with ischemic cardiomyopathy, atrial fibrillation and a history of valvular heart disease status post TAVR developed abdominal pain post-operatively. The patient was found to have ischemic bowel and died on post-operative day two. The death was adjudicated as procedure-related but not device-related. Another patient died of sudden cardiac arrest on day 29 after the procedure. CEC adjudicated the death as not device- or procedure-related.

Adverse Events

Table 15 presents a summary of adverse events as reported by investigators. There were no unanticipated adverse device effects. Tables 16 and 17 present the serious and non-serious adverse device effects reported in the pivotal study.

Table 15. Summary of Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
Adverse Event Class	**Events [Rate[1]]**	**Percent of Subjects with Event**	**Events [Rate[1]]**	**Percent of Subjects with Event**
SAE	729 [157.3]	56.7% (282/497)	799 [171.3]	53.3% (268/503)
ADE	16 [3.45]	3.0% (15/497)	20 [4.29]	4.0% (20/503)
SADE	9 [1.94]	1.8% (9/497)	15 [3.22]	2.4% (12/503)
UADE	0 [0.00]	0.0% (0/497)	0 [0.00]	0.0% (0/503)

1. Rate is number of events per 100 subject years.

Table 16. Summary of Serious Adverse Device Effects (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate[1]]**	**Percent of Subjects with Event**	**Events [Rate[1]]**	**Percent of Subjects with Event**
Overall Follow-Up				

Table 16. Summary of Serious Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N=497)		Control (N=503)	
	Events [Rate[1]]	Percent of Subjects with Event	Events [Rate[1]]	Percent of Subjects with Event
Cardiac Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Arrhythmia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Cardiac Failure Congestive	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
General Disorders and Administration Site Conditions[2]	**4 [0.86]**	**0.8% (4/497)**	**4 [0.86]**	**0.8% (4/503)**
Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	1 [0.21]	0.2% (1/503)
Device Deployment Issue[3]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Device Dislocation[4]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	**1 [0.22]**	**0.2% (1/497)**	**2 [0.43]**	**0.4% (2/503)**
Arterial Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	**0 [0.00]**	**0.0% (0/497)**	**6 [1.29]**	**1.0% (5/503)**
Hemoptysis	0 [0.00]	0.0% (0/497)	4 [0.86]	0.6% (3/503)
Pulmonary Embolism	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Vascular Disorders	**2 [0.43]**	**0.4% (2/497)**	**3 [0.64]**	**0.6% (3/503)**
Embolism	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hematoma	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Thrombosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	**9 [1.94]**	**1.8% (9/497)**	**15 [3.22]**	**2.4% (12/503)**

1. Rate is number of events per 100 subject years.
2. Administration Site Conditions refers to events associated with site at which the device is administered
3. Device did not completely detach from delivery catheter upon initial deployment, but was ultimately deployed and confirmed to be working successfully.
4. Partial dislodgement of a left ventricular pacemaker lead during the CardioMEMS™ device implantation procedure, requiring subsequent lead revision. All SADEs occurred in NYHA Class II/III subjects prior to COVID-19.

Table 17. Summary of Adverse Device Effects (As Reported by Investigator)

System Organ Class Preferred Term	Treatment (N=497)		Control (N=503)	
	Events [Rate[1]]	Percent of Subjects with Event	Events [Rate[1]]	Percent of Subjects with Event
Cardiac Disorders	**0 [0.00]**	**0.0% (0/497)**	**2 [0.43]**	**0.4% (2/503)**
Arrhythmia	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
General Disorders and Administration Site Conditions	**9 [1.94]**	**1.8% (9/497)**	**18 [3.86]**	**3.6% (18/503)**
Catheter Site Hematoma	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Catheter Site Hemorrhage	4 [0.86]	0.8% (4/497)	6 [1.29]	1.2% (6/503)
Device Deployment Issue	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)

Table 17. Summary of Adverse Device Effects (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate[1]]**	**Percent of Subjects with Event**	**Events [Rate[1]]**	**Percent of Subjects with Event**
Device Dislocation	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
Device Information Output Issue	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Device Malfunction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pyrexia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Vessel Puncture Site Pain	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Injury, Poisoning and Procedural Complications	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Arterial Injury	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Nervous System Disorders	**1 [0.22]**	**0.2% (1/497)**	**0 [0.00]**	**0.0% (0/503)**
Presyncope	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Respiratory, Thoracic and Mediastinal Disorders	**3 [0.65]**	**0.6% (3/497)**	**0 [0.00]**	**0.0% (0/503)**
Hemoptysis	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Vascular Disorders	**1 [0.22]**	**0.2% (1/497)**	**0 [0.00]**	**0.0% (0/503)**
Hypotension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Total	**16 [3.45]**	**3.0% (15/497)**	**20 [4.29]**	**4.0% (20/503)**

Note: All ADEs occurred in NYHA Class II/III subjects prior to COVID-19.

1. Rate is number of events per 100 subject years.

Note: Rate is number of events per 100 subject years

Serious Adverse Events

A serious adverse event (SAE) was defined as an adverse event not related to the use of the device but meeting seriousness criteria (requiring hospitalization or invasive intervention or resulting in a life-threatening illness or injury). A summary of non-device-related investigator-reported SAEs is provided in the table below.

Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Blood and Lymphatic System Disorders	**11 [2.37]**	**1.6% (8/497)**	**8 [1.72]**	**1.4% (7/503)**
Anemia	9 [1.94]	1.2% (6/497)	8 [1.72]	1.4% (7/503)
Thrombocytopenia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Cardiac Disorders	**302 [65.2]**	**32.6% (162/497)**	**389 [83.4]**	**38.8% (195/503)**
Acute Myocardial Infarction	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Angina Pectoris	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Angina Unstable	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Aortic Valve Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Arrhythmia	53 [11.4]	9.5% (47/497)	54 [11.6]	9.1% (46/503)
Atrioventricular Block Complete	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Aneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Arrest	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
Cardiac Failure Congestive	216 [46.6]	26.2% (130/497)	276 [59.2]	30.8% (155/503)
Cardiac Perforation	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cardiac Valve Disease	1 [0.22]	0.2% (1/497)	4 [0.86]	0.6% (3/503)
Cardiogenic Shock	8 [1.73]	1.6% (8/497)	6 [1.29]	1.0% (5/503)
Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Coronary Artery Disease	1 [0.22]	0.2% (1/497)	9 [1.93]	1.6% (8/503)
Intracardiac Thrombus	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Ischemic Cardiomyopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Mitral Valve Disease	1 [0.22]	0.2% (1/497)	3 [0.64]	0.4% (2/503)
Mitral Valve Incompetence	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Myocardial Infarction	11 [2.37]	2.0% (10/497)	16 [3.43]	3.2% (16/503)
Pericardial Effusion	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Pericarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Prinzmetal Angina	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Restrictive Cardiomyopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Tachycardia	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Ear and Labyrinth Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Vertigo	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vertigo Positional	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Endocrine Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Hypothyroidism	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Inappropriate Antidiuretic Hormone Secretion	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastrointestinal Disorders	**29 [6.26]**	**4.8% (24/497)**	**33 [7.08]**	**5.0% (25/503)**
Abdominal Pain	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Colitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Colitis Ischemic	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Colonic Stenosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Constipation	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
Diarrhea	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)

Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Duodenal Ulcer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Dysphagia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Gastritis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Gastrointestinal Hemorrhage	10 [2.16]	1.8% (9/497)	20 [4.29]	3.2% (16/503)
Gastrointestinal Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastroesophageal Reflux Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hemorrhoidal Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Ileus	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Impaired Gastric Emptying	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Intestinal Ischemia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nausea	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pancreatic Mass	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pancreatitis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Pancreatitis Acute	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Proctitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Small Intestinal Obstruction	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Spigelian Hernia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vomiting	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
General Disorders and Administration Site Conditions[1]	**49 [10.6]**	**8.2% (41/497)**	**34 [7.29]**	**6.2% (31/503)**
Accidental Death[2]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Asthenia	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
Catheter Site Hematoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Chest Pain	32 [6.90]	5.4% (27/497)	25 [5.36]	4.6% (23/503)
Death[3]	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Device Dislocation[4]	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Device Electrical Impedance Issue[5]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Device Malfunction[6]	0 [0.00]	0.0% (0/497)	3 [0.64]	0.6% (3/503)
Fatigue	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Generalized Edema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hypothermia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Implant Site Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Multi-Organ Failure	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Polyp	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Sudden Cardiac Death[7]	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hepatobiliary Disorders	**4 [0.86]**	**0.8% (4/497)**	**4 [0.86]**	**0.8% (4/503)**
Cholangitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cholelithiasis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hepatic Cirrhosis	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Hepatic Function Abnormal	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Ischemic Hepatitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Immune System Disorders	**0 [0.00]**	**0.0% (0/497)**	**2 [0.43]**	**0.4% (2/503)**

1. Administration Site Conditions refers to events associated with site at which the device is administered.
2. Traumatic death in an accident.
3. Unknown event leading to death.
4. Hip prosthesis dislocation, unrelated to study device.
5. Broken pacemaker lead, unrelated to study device.
6. Cardiac pacemaker or ICD malfunction, unrelated to study device.
7. Sudden cardiac death due to ischemic heart disease.

Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Drug Hypersensitivity	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Heart Transplant Rejection	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Infections and Infestations	**99 [21.4]**	**15.3% (76/497)**	**113 [24.2]**	**16.9% (85/503)**
Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Anal Abscess	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Bronchitis	2 [0.43]	0.4% (2/497)	7 [1.50]	1.4% (7/503)
Cellulitis	6 [1.29]	1.0% (5/497)	8 [1.72]	1.4% (7/503)
Central Nervous System Abscess	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Clostridial Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Coronavirus Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Cystitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Endocarditis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Gastroenteritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastroenteritis Viral	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Gastrointestinal Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Herpes Zoster	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Infection	29 [6.26]	5.4% (27/497)	39 [8.36]	6.8% (34/503)
Influenza	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
Intervertebral Discitis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Mycotic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pneumonia	27 [5.83]	4.8% (24/497)	32 [6.86]	5.8% (29/503)
Sepsis	18 [3.88]	3.4% (17/497)	10 [2.14]	2.0% (10/503)
Septic Shock	0 [0.00]	0.0% (0/497)	4 [0.86]	0.8% (4/503)
Upper Respiratory Tract Infection	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Urinary Tract Infection	3 [0.65]	0.6% (3/497)	4 [0.86]	0.8% (4/503)
Wound Infection	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Injury, Poisoning and Procedural Complications	**15 [3.24]**	**2.8% (14/497)**	**16 [3.43]**	**3.0% (15/503)**
Cervical Vertebral Fracture	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Fall	4 [0.86]	0.8% (4/497)	6 [1.29]	1.0% (5/503)
Femur Fracture	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hip Fracture	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Iliotibial Band Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Joint Injury	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Laceration	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Multiple Fractures	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pelvic Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Road Traffic Accident[1]	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Spinal Compression Fracture	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Spinal Fracture	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Subdural Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Vascular Pseudoaneurysm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Investigations	**21 [4.53]**	**3.8% (19/497)**	**21 [4.50]**	**3.0% (15/503)**
Anticoagulation Drug Level Below Therapeutic	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Blood Creatinine Increased	18 [3.88]	3.4% (17/497)	17 [3.65]	2.6% (13/503)
International Normalized Ratio Decreased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

1. Multiple injuries and surgical procedures resulting from a motor vehicle accident.

Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
International Normalized Ratio Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Left Ventricular End-Diastolic Pressure Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Transaminases Increased	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Troponin Increased	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Metabolism and Nutrition Disorders	**25 [5.39]**	**4.8% (24/497)**	**24 [5.15]**	**4.0% (20/503)**
Dehydration	8 [1.73]	1.6% (8/497)	2 [0.43]	0.4% (2/503)
Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Diabetic Ketoacidosis	0 [0.00]	0.0% (0/497)	2 [0.43]	0.4% (2/503)
Fluid Overload	2 [0.43]	0.4% (2/497)	2 [0.43]	0.2% (1/503)
Gout	2 [0.43]	0.4% (2/497)	2 [0.43]	0.4% (2/503)
Hyperglycemia	5 [1.08]	1.0% (5/497)	5 [1.07]	0.8% (4/503)
Hyperkalemia	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Hypoglycemia	2 [0.43]	0.4% (2/497)	4 [0.86]	0.8% (4/503)
Hypokalemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Hypovolemia	1 [0.22]	0.2% (1/497)	3 [0.64]	0.6% (3/503)
Lactic Acidosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Type 2 Diabetes Mellitus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Musculoskeletal and Connective Tissue Disorders	**14 [3.02]**	**2.4% (12/497)**	**4 [0.86]**	**0.8% (4/503)**
Arthralgia	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Back Pain	5 [1.08]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Compartment Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Fibromyalgia	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Muscular Weakness	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Myopathy	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Osteoarthritis	2 [0.43]	0.4% (2/497)	1 [0.21]	0.2% (1/503)
Rhabdomyolysis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Rheumatoid Arthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Spinal Osteoarthritis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**2 [0.43]**	**0.4% (2/497)**	**2 [0.43]**	**0.4% (2/503)**
Colon Cancer	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Lung Neoplasm	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Esophageal Adenocarcinoma	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Squamous Cell Carcinoma	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nervous System Disorders	**42 [9.06]**	**7.4% (37/497)**	**28 [6.00]**	**4.8% (24/503)**
Carotid Artery Stenosis	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Cerebrovascular Accident	12 [2.59]	2.2% (11/497)	6 [1.29]	1.2% (6/503)
Cerebrovascular Disorder	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cervicogenic Headache	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
CNS Ventriculitis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Complicated Migraine	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Convulsion	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Dizziness	4 [0.86]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hemorrhage Intracranial	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Headache	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Hepatic Encephalopathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hypoesthesia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Metabolic Encephalopathy	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Myoclonus	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Partial Seizures	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Presyncope	3 [0.65]	0.6% (3/497)	0 [0.00]	0.0% (0/503)
Sciatica	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Subarachnoid Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Syncope	12 [2.59]	2.4% (12/497)	8 [1.72]	1.6% (8/503)
Transient Ischemic Attack	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Vertebral Artery Stenosis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Psychiatric Disorders	**3 [0.65]**	**0.6% (3/497)**	**6 [1.29]**	**1.0% (5/503)**
Depression	0 [0.00]	0.0% (0/497)	3 [0.64]	0.4% (2/503)
Mental Disorder	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Mental Status Changes	2 [0.43]	0.4% (2/497)	3 [0.64]	0.6% (3/503)
Renal and Urinary Disorders	**29 [6.26]**	**4.8% (24/497)**	**41 [8.79]**	**7.6% (38/503)**
Hematuria	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Nephrolithiasis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Obstructive Uropathy	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Renal Failure	3 [0.65]	0.6% (3/497)	1 [0.21]	0.2% (1/503)
Renal Failure Acute	21 [4.53]	3.6% (18/497)	29 [6.22]	5.6% (28/503)
Renal Failure Chronic	2 [0.43]	0.4% (2/497)	6 [1.29]	1.0% (5/503)
Urinary Retention	3 [0.65]	0.6% (3/497)	2 [0.43]	0.4% (2/503)
Reproductive System and Breast Disorders	**1 [0.22]**	**0.2% (1/497)**	**1 [0.21]**	**0.2% (1/503)**
Benign Prostatic Hyperplasia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Vaginal Hemorrhage	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Respiratory, Thoracic and Mediastinal Disorders	**42 [9.06]**	**6.8% (34/497)**	**52 [11.2]**	**7.6% (38/503)**
Acute Respiratory Failure	3 [0.65]	0.6% (3/497)	8 [1.72]	1.6% (8/503)
Asthma	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Chronic Obstructive Pulmonary Disease	13 [2.80]	1.8% (9/497)	24 [5.15]	2.8% (14/503)
Chronic Respiratory Disease	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Cough	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Dyspnea	7 [1.51]	1.4% (7/497)	8 [1.72]	1.6% (8/503)
Epistaxis	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Hemoptysis	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Hypoxia	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pleural Effusion	5 [1.08]	0.8% (4/497)	4 [0.86]	0.8% (4/503)
Pneumothorax	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Pulmonary Alveolar Hemorrhage	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Pulmonary Embolism	1 [0.22]	0.2% (1/497)	1 [0.21]	0.2% (1/503)
Pulmonary Hypertension	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Respiratory Failure	4 [0.86]	0.8% (4/497)	3 [0.64]	0.6% (3/503)
Sleep Apnea Syndrome	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)

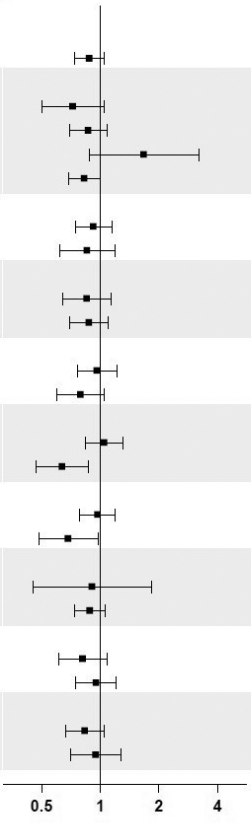
Table 18. Summary of Serious Adverse Events (As Reported by Investigator)

	Treatment (N=497)		Control (N=503)	
System Organ Class Preferred Term	**Events [Rate]**	**Percent of Subjects with Event**	**Events [Rate]**	**Percent of Subjects with Event**
Skin and Subcutaneous Tissue Disorders	**2 [0.43]**	**0.4% (2/497)**	**0 [0.00]**	**0.0% (0/503)**
Angioedema	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hyperhidrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Surgical and Medical Procedures	**0 [0.00]**	**0.0% (0/497)**	**1 [0.21]**	**0.2% (1/503)**
Cardiac Pacemaker Replacement	0 [0.00]	0.0% (0/497)	1 [0.21]	0.2% (1/503)
Vascular Disorders	**35 [7.55]**	**5.0% (25/497)**	**20 [4.29]**	**3.6% (18/503)**
Aortic Aneurysm	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Bleeding Varicose Vein	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Embolism	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Extremity Necrosis	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hematoma	2 [0.43]	0.4% (2/497)	0 [0.00]	0.0% (0/503)
Hypertension	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Hypertensive Crisis	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Hypotension	14 [3.02]	2.6% (13/497)	11 [2.36]	2.2% (11/503)
Lymphoedema	2 [0.43]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Orthostatic Hypotension	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Peripheral Arterial Occlusive Disease	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Peripheral Vascular Disorder	1 [0.22]	0.2% (1/497)	2 [0.43]	0.4% (2/503)
Shock	1 [0.22]	0.2% (1/497)	0 [0.00]	0.0% (0/503)
Thrombosis	5 [1.08]	0.8% (4/497)	3 [0.64]	0.4% (2/503)
Total	**729 [157.3]**	**56.7% (282/497)**	**799 [171.3]**	**53.3% (268/503)**

Subgroup Analyses

The primary endpoint was evaluated in subgroups of NYHA Class, qualifying category, ejection fraction, age, sex, race, ethnicity, ischemic cardiomyopathy, and prior cardiac device implant. Figures 8 and 9 show the forest plots for all follow-up and pre-COVID-19, respectively. Women notably derived more benefit than men with 36% reduction in primary endpoint events. African American subjects also gained a larger treatment effect, though minorities (African American and Hispanic subjects) in both the Treatment group and the Control group experienced high rates of primary endpoint events.

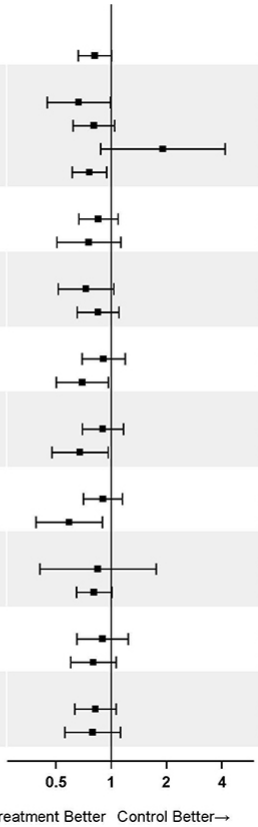
Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Subgroup p-value	Interaction p-value
Overall	1000	253 (0.563)	289 (0.640)	0.88 (0.74, 1.05)	0.16	
NYHA Class						
NYHA Class II	296	53 (0.401)	75 (0.554)	0.72 (0.50, 1.05)	0.086	0.095
NYHA Class III*	650	171 (0.589)	198 (0.677)	0.87 (0.70, 1.08)	0.21	
NYHA Class IV	54	29 (1.527)	16 (0.910)	1.68 (0.88, 3.20)	0.12	
NYHA Class II and III	946	224 (0.525)	273 (0.633)	0.83 (0.69, 1.00)	0.050	0.046†
Qualification						
HFH in year prior	557	181 (0.757)	212 (0.820)	0.92 (0.74, 1.14)	0.47	0.71
Elevated BNP/NT pro-BNP only	442	72 (0.350)	77 (0.409)	0.86 (0.62, 1.19)	0.36	
Ejection Fraction						
HFpEF (EF>40%)*	469	90 (0.442)	114 (0.518)	0.85 (0.64, 1.14)	0.28	0.90
HFrEF (EF≤40%)*	531	163 (0.677)	175 (0.773)	0.88 (0.70, 1.10)	0.26	
Age						
Below Median (<71 Years)*	492	156 (0.730)	173 (0.758)	0.96 (0.76, 1.22)	0.75	0.30
Median and Above (≥71 Years)*	508	97 (0.420)	116 (0.529)	0.79 (0.60, 1.05)	0.11	
Sex						
Men*	625	178 (0.656)	171 (0.625)	1.05 (0.84, 1.31)	0.67	0.010
Women*	375	75 (0.434)	118 (0.681)	0.64 (0.47, 0.87)	0.004	
Race						
Caucasian*	807	189 (0.516)	194 (0.531)	0.97 (0.79, 1.20)	0.78	0.095
African American*	179	60 (0.811)	94 (1.184)	0.68 (0.48, 0.97)	0.035	
Ethnicity						
Hispanic*	33	18 (1.257)	21 (1.383)	0.91 (0.45, 1.83)	0.79	0.95
Non-Hispanic*	960	232 (0.544)	264 (0.615)	0.88 (0.73, 1.07)	0.20	
Ischemic Cardiomyopathy						
Ischemic*	397	99 (0.545)	112 (0.670)	0.81 (0.61, 1.08)	0.16	0.40
Non-Ischemic*	560	142 (0.578)	160 (0.607)	0.95 (0.75, 1.21)	0.69	
Device Implant						
With CRT-D/CRT-P/ICD*	562	162 (0.633)	188 (0.759)	0.83 (0.67, 1.04)	0.11	0.48
Without CRT-D/CRT-P/ICD *	438	91 (0.482)	101 (0.508)	0.95 (0.71, 1.28)	0.73	



*Pre-specified subgroup
†Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Figure 8. Subgroup Analyses – All Follow-up

Subgroup	N	Treatment Events (Rate)	Control Events (Rate)	HR (95% CI)	Interaction p-value
Overall	1000	177 (0.595)	224 (0.730)	0.81 (0.66, 1.00)	
NYHA Class					
NYHA Class II	296	43 (0.393)	70 (0.591)	0.67 (0.45, 0.99)	0.074
NYHA Class III	650	114 (0.552)	141 (0.686)	0.80 (0.62, 1.04)	
NYHA Class IV	54	20 (3.123)	13 (1.632)	1.91 (0.88, 4.18)	
NYHA Class II and III	946	157 (0.497)	211 (0.653)	0.76 (0.61, 0.95)	0.035*
Qualification					
HFH in year prior	557	133 (0.771)	166 (0.905)	0.85 (0.67, 1.09)	0.58
Elevated BNP/NT pro-BNP only	442	44 (0.358)	58 (0.474)	0.76 (0.51, 1.13)	
Ejection Fraction					
HFpEF (EF>40%)	469	57 (0.401)	85 (0.551)	0.73 (0.51, 1.03)	0.50
HFrEF (EF≤40%)	531	120 (0.738)	139 (0.870)	0.85 (0.65, 1.10)	
Age					
Below Median (<71 Years)	492	112 (0.746)	130 (0.820)	0.91 (0.69, 1.19)	0.22
Median and Above (≥71 Years)	508	65 (0.442)	94 (0.635)	0.70 (0.50, 0.97)	
Sex					
Men	625	121 (0.687)	139 (0.763)	0.90 (0.70, 1.17)	0.21
Women	375	56 (0.462)	85 (0.683)	0.68 (0.48, 0.96)	
Race					
White	807	135 (0.607)	154 (0.673)	0.90 (0.71, 1.15)	0.091
Black	179	38 (0.721)	70 (1.221)	0.59 (0.39, 0.89)	
Ethnicity					
Hispanic	33	17 (1.575)	19 (1.860)	0.85 (0.41, 1.76)	0.84
Non-Hispanic	960	157 (0.586)	202 (0.726)	0.81 (0.65, 1.01)	
Ischemic Cardiomyopathy					
Ischemic	397	83 (0.682)	87 (0.760)	0.90 (0.65, 1.24)	0.61
Non-Ischemic	560	91 (0.526)	125 (0.658)	0.80 (0.60, 1.06)	
Device Implant					
With CRT-D/CRT-P/ICD	562	117 (0.776)	144 (0.945)	0.82 (0.63, 1.06)	0.92
Without CRT-D/CRT-P/ICD	438	60 (0.424)	80 (0.535)	0.79 (0.56, 1.12)	



*Interaction p-value testing Randomization Group by NYHA Class II and III vs. Class IV

Figure 9. Subgroup Analyses – Prior to COVID-19

Within the subgroup analyses, an interaction was observed for NYHA class, with the subgroup of NYHA Class IV patients (N = 54) demonstrating a different treatment effect than NYHA Class II and/or III patients. NYHA Class II/III patients overall demonstrated a 24% reduction in primary endpoint events prior to COVID-19 (HR 0.76, 95% CI 0.61-0.95) while NYHA Class IV patients did worse with hemodynamic-guided HF therapy during the same period (HR 1.91, CI 0.88-4.18). The NYHA Class sensitivity analysis demonstrated an interaction p-value of p=0.035, and separate analysis for each NYHA Class is provided below.

NYHA Class II

The baseline demographics and key characteristics for the NYHA Class II patients in the Treatment group and the Control group were balanced and listed in the table below.

Table 19. Demographics and Baseline Assessments – NYHA Class II Subjects

	Treatment (N=146)	**Control (N=150)**
Age – yr	69.8 ± 10.9 (146)	69.8 ± 10.5 (150)
Female Sex	33.6% (49/146)	34.0% (51/150)
Race		
White	84.2% (123/146)	82.0% (123/150)
Black	15.1% (22/146)	17.3% (26/150)
Other	0.7% (1/146)	0.7% (1/150)
Ethnicity		
Hispanic	2.7% (4/146)	4.0% (6/150)
Non-Hispanic	95.2% (139/146)	96.0% (144/150)
Unknown	2.1% (3/146)	0.0% (0/150)
Body mass index – kg/m^2	30.7 ± 7.3 (146)	32.5 ± 7.4 (150)
Medical History		
Ischemic etiology	43.2% (63/146)	45.3% (68/150)
Diabetes	49.3% (72/146)	44.7% (67/150)
Atrial flutter or fibrillation	56.8% (83/146)	58.0% (87/150)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction – %	39.2 ± 17.2 (146)	39.8 ± 16.1 (150)
Left ventricular ejection fraction >40%	42.5% (62/146)	44.0% (66/150)
Pulmonary capillary wedge pressure – mmHg	16.9 ± 8.2 (145)	17.7 ± 8.4 (150)
Cardiac output – L/min	4.61 ± 1.30 (146)	4.51 ± 1.10 (150)
Cardiac index – L/min/m^2	2.27 ± 0.61 (146)	2.14 ± 0.48 (150)
Laboratory Analyses		
Serum creatinine level – µmol/L	123.1 ± 40.7 (146)	128.3 ± 44.7 (144)
Estimated glomerular filtration rate – ml/min/1.73m^2	56.7 ± 21.5 (146)	54.6 ± 19.2 (143)
B-type natriuretic peptide level – pg/mL	472.8 ± 480.3 (61)	525.4 ± 727.7 (69)
N-terminal pro-B-type natriuretic peptide level – pg/mL	2526 ± 3842 (76)	1537 ± 985 (72)
Treatment History		
Previous cardiac resynchronization therapy	26.7% (39/146)	35.3% (53/150)
Previous implantation of defibrillator	49.3% (72/146)	40.0% (60/150)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	69.2% (101/146)	70.0% (105/150)
ARNi	32.9% (48/146)	30.0% (45/150)
Beta Blocker	89.7% (131/146)	91.3% (137/150)
Mineralocorticoid Receptor Antagonist	43.2% (63/146)	33.3% (50/150)
Diuretic	90.4% (132/146)	93.3% (140/150)
Hydralazine	11.6% (17/146)	20.0% (30/150)
Nitrate	17.8% (26/146)	16.7% (25/150)
SGLT2 Inhibitor	2.2% (1/46)	0.0% (0/41)
Enrollment Type		
Heart failure hospitalization in year prior only	32.2% (47/146)	32.7% (49/150)
Elevated natriuretic peptide level in 30 day prior only	50.7% (74/146)	49.3% (74/150)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	17.1% (25/146)	18.0% (27/150)

Table 19. Demographics and Baseline Assessments – NYHA Class II Subjects

	Treatment (N=146)	Control (N=150)
Patient Reported Outcomes		
KCCQ-12 at Baseline – Overall Summary Score	69.7 ± 20.7 (145)	66.4 ± 20.5 (147)
6MHW as Baseline – m	285.5 ± 111.3 (142)	264.8 ± 120.3 (146)

Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

The primary endpoint event rates and components for NYHA Class II subjects for the full follow-up and prior to COVID-19 are presented in the table below. Before the pandemic, there were 43 primary endpoint events in the Treatment group compared with 70 events in the Control group, representing a 33% reduction in the 12-month rate of primary endpoint events (0.393 events per patient in the Treatment group vs. 0.591 events per patient in the Control group, HR 0.67)

Table 20. Primary Endpoint and Components – NYHA Class II Subjects

Endpoint[1]	Treatment (N=146) Events (Rate[2])	Control (N=150) Events (Rate[2])	Hazard Ratio (95% CI)[3]
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**53 (0.401)**	**75 (0.554)**	**0.72 (0.50, 1.05)**
Heart Failure Hospitalization + ED/OP	42 (0.317)	67 (0.493)	0.64 (0.43, 0.96)
Heart Failure Hospitalization	39 (0.298)	56 (0.417)	0.71 (0.47, 1.09)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	3 (0.025)	11 (0.089)	0.28 (0.08, 0.99)
Death	11 (0.086)	8 (0.061)	1.39 (0.56, 3.46)
Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.1579
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**43 (0.393)**	**70 (0.591)**	**0.67 (0.45, 0.99)**
Heart Failure Hospitalization + ED/OP	33 (0.307)	62 (0.531)	0.58 (0.37, 0.89)
Heart Failure Hospitalization	30 (0.276)	51 (0.433)	0.64 (0.40, 1.01)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	3 (0.038)	11 (0.128)	0.30 (0.08, 1.06)
Death	10 (0.099)	8 (0.074)	1.34 (0.53, 3.39)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
2. Event Rate is an annualized rate estimated from the Andersen-Gill model.
3. Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
4. Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

NYHA Class III

Table 21 presents the baseline demographics and key characteristics for the NYHA Class III patients in the Treatment group and the Control group.

Table 21. Demographics and Baseline Assessments – NYHA Class III Subjects

	Treatment (N=322)	Control (N=328)
Age – yr	68.8 ± 11.3 (322)	69.0 ± 11.2 (328)
Female Sex	39.8% (128/322)	38.7% (127/328)
Race		
White	80.7% (260/322)	79.6% (261/328)
Black	17.7% (57/322)	19.5% (64/328)
Other	1.8% (6/322)	1.2% (4/328)
Ethnicity		
Hispanic	3.7% (12/322)	2.7% (9/328)
Non-Hispanic	96.0% (309/322)	96.6% (317/328)
Unknown	0.3% (1/322)	0.6% (2/328)
Body mass index – kg/m^2	33.9 ± 8.4 (322)	34.2 ± 8.5 (328)

Table 21. Demographics and Baseline Assessments – NYHA Class III Subjects

	Treatment (N=322)	Control (N=328)
Medical History		
Ischemic etiology	40.7% (131/322)	35.1% (115/328)
Diabetes	48.1% (155/322)	56.1% (184/328)
Atrial flutter or fibrillation	61.8% (199/322)	57.9% (190/328)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction – %	39.9 ± 17.2 (322)	41.0 ± 17.3 (328)
Left ventricular ejection fraction >40%	47.2% (152/322)	50.6% (166/328)
Pulmonary capillary wedge pressure – mmHg	17.2 ± 7.9 (321)	17.4 ± 7.6 (328)
Cardiac output – L/min	4.96 ± 3.11 (322)	4.76 ± 1.59 (328)
Cardiac index – L/min/m^2	2.29 ± 1.30 (322)	2.20 ± 0.67 (328)
Laboratory Analyses		
Serum creatinine level – µmol/L	129.1 ± 44.2 (320)	134.5 ± 49.3 (326)
Estimated glomerular filtration rate – ml/min/1.73m^2	53.7 ± 21.0 (320)	52.5 ± 21.6 (326)
B-type natriuretic peptide level – pg/mL	550.8 ± 763.1 (181)	573.9 ± 1054.3 (176)
N-terminal pro-B-type natriuretic peptide level – pg/mL	2258 ± 3316 (133)	2431 ± 3235 (140)
Treatment History		
Previous cardiac resynchronization therapy	28.3% (91/322)	30.5% (100/328)
Previous implantation of defibrillator	40.4% (130/322)	41.5% (136/328)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	62.1% (200/322)	61.9% (203/328)
ARNi	27.3% (88/322)	26.5% (87/328)
Beta Blocker	89.8% (289/322)	87.2% (286/328)
Mineralocorticoid Receptor Antagonist	49.7% (160/322)	46.3% (152/328)
Diuretic	97.2% (313/322)	95.7% (314/328)
Hydralazine	17.4% (56/322)	14.0% (46/328)
Nitrate	20.8% (67/322)	22.6% (74/328)
SGLT2 Inhibitor	1.0% (1/98)	2.2% (2/92)
Enrollment Type		
Heart failure hospitalization in year prior only	35.7% (115/322)	40.1% (131/327)
Elevated natriuretic peptide level in 30 day prior only	44.4% (143/322)	40.4% (132/327)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	19.9% (64/322)	19.6% (64/327)
Patient Reported Outcomes		
KCCQ-12 at Baseline – Overall Summary Score	49.7 ± 23.1 (320)	50.7 ± 23.3 (325)
6MHW as Baseline – m	218.9 ± 116.1 (306)	218.1 ± 121.4 (312)

Note: Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)

Table 22 presents the primary endpoint event rates and components for NYHA Class III subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 114 primary endpoint events in the Treatment group compared with 141 events in the Control group. The difference represents a 20% reduction in the 12-month rate of primary endpoint events (0.552 events per patient in the Treatment group vs. 0.686 events per patient in the Control group, HR 0.80).

Table 22. Primary Endpoint and Components – NYHA Class III Subjects

Endpoint[1]	Treatment (N=322) Events (Rate[2])	Control (N=328) Events (Rate[2])	Hazard Ratio (95% CI)[3]
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**171 (0.589)**	**198 (0.677)**	**0.87 (0.70, 1.08)**
Heart Failure Hospitalization + ED/OP	147 (0.502)	171 (0.580)	0.86 (0.69, 1.09)
Heart Failure Hospitalization	127 (0.431)	156 (0.526)	0.82 (0.64, 1.04)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	20 (0.073)	15 (0.054)	1.34 (0.68, 2.62)
Death	24 (0.089)	27 (0.100)	0.90 (0.52, 1.55)

Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.2840
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**114 (0.552)**	**141 (0.686)**	**0.80 (0.62, 1.04)**
Heart Failure Hospitalization + ED/OP	96 (0.460)	126 (0.606)	0.76 (0.58, 1.00)
Heart Failure Hospitalization	81 (0.389)	115 (0.555)	0.70 (0.52, 0.94)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	15 (0.077)	11 (0.057)	1.36 (0.62, 2.97)
Death	18 (0.108)	15 (0.091)	1.19 (0.60, 2.36)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
2. Event Rate is an annualized rate estimated from the Andersen-Gill model.
3. Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
4. Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

NYHA Class IV

Table 23 presents the baseline demographics and key characteristics for the NYHA Class IV patients (N = 54).

Table 23. Demographics and Baseline Assessments – NYHA Class IV Subjects		
	Treatment (N=29)	**Control (N=25)**
Age – yr	70.3 ± 8.8 (29)	67.3 ± 12.2 (25)
Female Sex	34.5% (10/29)	40.0% (10/25)
Race		
White	69.0% (20/29)	84.0% (21/25)
Black	27.6% (8/29)	12.0% (3/25)
Other	3.4% (1/29)	4.0% (1/25)
Ethnicity		
Hispanic	0.0% (0/29)	8.0% (2/25)
Non-Hispanic	100.0% (29/29)	88.0% (22/25)
Unknown	0.0% (0/29)	4.0% (1/25)
Body mass index – kg/m2	33.4 ± 10.0 (29)	37.0 ± 11.2 (25)
Medical History		
Ischemic etiology	44.8% (13/29)	28.0% (7/25)
Diabetes	55.2% (16/29)	40.0% (10/25)
Atrial flutter or fibrillation	62.1% (18/29)	56.0% (14/25)
Vital Signs and Hemodynamic Analyses		
Left ventricular ejection fraction – %	34.1 ± 17.8 (29)	42.2 ± 16.7 (25)
Left ventricular ejection fraction >40%	34.5% (10/29)	52.0% (13/25)
Pulmonary capillary wedge pressure – mmHg	19.6 ± 9.1 (29)	18.5 ± 8.5 (25)
Cardiac output – L/min	4.40 ± 1.16 (29)	4.98 ± 1.61 (25)
Cardiac index – L/min/m2	2.08 ± 0.53 (29)	2.23 ± 0.74 (25)
Laboratory Analyses		
Serum creatinine level – µmol/L	148.9 ± 58.7 (29)	149.9 ± 56.2 (25)
Estimated glomerular filtration rate – ml/min/1.73m2	49.3 ± 23.0 (29)	45.3 ± 17.2 (25)
B-type natriuretic peptide level – pg/mL	386.8 ± 482.7 (19)	378.9 ± 329.9 (11)
N-terminal pro-B-type natriuretic peptide level – pg/mL	4653 ± 6525 (10)	3092 ± 3946 (13)
Treatment History		
Previous cardiac resynchronization therapy	41.4% (12/29)	40.0% (10/25)
Previous implantation of defibrillator	37.9% (11/29)	36.0% (9/25)
Guideline-Directed Medical Therapy		
ACE-Inhibitor or ARB or ARNi	62.1% (18/29)	48.0% (12/25)
ARNi	31.0% (9/29)	28.0% (7/25)
Beta Blocker	82.8% (24/29)	76.0% (19/25)
Mineralocorticoid Receptor Antagonist	48.3% (14/29)	56.0% (14/25)

Table 23. Demographics and Baseline Assessments – NYHA Class IV Subjects		
	Treatment (N=29)	**Control (N=25)**
Diuretic	100.0% (29/29)	96.0% (24/25)
Hydralazine	27.6% (8/29)	16.0% (4/25)
Nitrate	20.7% (6/29)	16.0% (4/25)
SGLT2 Inhibitor	0.0% (0/8)	0.0% (0/7)
Enrollment Type		
Heart failure hospitalization in year prior only	27.6% (8/29)	44.0% (11/25)
Elevated natriuretic peptide level in 30 day prior only	44.8% (13/29)	24.0% (6/25)
Heart failure hospitalization in year prior and elevated natriuretic peptide level in 30 day prior	27.6% (8/29)	32.0% (8/25)
Patient Reported Outcomes		
KCCQ-12 at Baseline – Overall Summary Score	39.0 ± 20.2 (29)	40.5 ± 22.5 (25)
6MHW as Baseline – m	153.2 ± 119.3 (26)	164.4 ± 108.2 (24)
Continuous Variables: Mean ± SD (n); Categorical Variables: Percent (n/N)		

Table 24 presents the primary endpoint event rates and components for NYHA Class IV subjects for the full follow-up and prior to COVID-19. Before the pandemic, there were 20 primary endpoint events in the Treatment group compared with 13 events in the Control group. The hazard ratio was 1.91 with a wide confidence interval.

Table 24. Primary Endpoint and Components – NYHA Class IV Subjects

Endpoint[1]	**Treatment (N=29) Events (Rate[2])**	**Control (N=25) Events (Rate[2])**	**Hazard Ratio (95% CI)[3]**
Full Follow-Up			
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**29 (1.527)**	**16 (0.910)**	**1.68 (0.88, 3.20)**
Heart Failure Hospitalization + ED/OP	24 (1.337)	14 (0.840)	1.59 (0.80, 3.18)
Heart Failure Hospitalization	19 (1.130)	13 (0.826)	1.37 (0.66, 2.84)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	5 (0.535)	1 (0.121)	4.43 (0.52, 38.0)
Death	5 (0.279)	2 (0.123)	2.26 (0.44, 11.6)
Prior to COVID-19			COVID-19 Interaction p-value[4], p=0.9455
Heart Failure Hospitalization + ED/OP + Death (Primary Endpoint)	**20 (3.123)**	**13 (1.632)**	**1.91 (0.88, 4.18)**
Heart Failure Hospitalization + ED/OP	18 (3.110)	11 (1.516)	2.05 (0.88, 4.77)
Heart Failure Hospitalization	13 (2.597)	10 (1.493)	1.74 (0.68, 4.43)
HF Emergency Department/Hospital Outpatient Visit (ED/OP)	5 (0.576)	1 (0.128)	4.51 (0.52, 38.9)
Death	2 (0.268)	2 (0.223)	1.20 (0.18, 8.15)

1. Endpoints include CEC adjudicated Heart Failure (HF) Hospitalizations or HF Emergency Department/Hospital Outpatient Visits (ED/OP) with an admission date after the date of implant hospitalization discharge through 395 days after the date of implant. All Cause Deaths are included from implant date to 395 days after implant date.
2. Event Rate is an annualized rate estimated from the Andersen-Gill model.
3. Hazard Ratio and 95% Confidence Interval estimated from the Andersen-Gill model with robust sandwich variance estimates.
4. Interaction p-value is a joint test on the interaction term of treatment group by COVID analysis time period.

Summary/Key Takeaways

Despite the limitations of COVID-19 occurring during the follow-up of the study, the results of the GUIDE-HF Randomized Arm support the continued safety and effectiveness of the CardioMEMS™ HF System within an expanded population, as shown by reduced HF hospitalizations. The treatment benefit observed in NYHA Class II subjects and those with elevated NT-proBNP/BNP but without a recent hospitalization for HF suggests that intervention in NYHA Class II heart failure, even prior to the occurrence of HF events, can provide benefit.

Pivotal Data from the CHAMPION Trial

The CHAMPION (CardioMEMS HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients) clinical trial was a prospective, multi-center, single-blind, randomized, clinical trial in 550 patients across 64 centers in the United States.

Purpose

The goal of the CHAMPION clinical trial was to determine if physicians could reduce HF hospitalizations by managing patient PA pressures using the CardioMEMS™ HF System.

Methods

Study Design

550 patients with NYHA Class III HF and a prior HF hospitalization within 12 months were randomized to standard of care plus the CardioMEMS HF System (Treatment group; 270 patients) or to standard of care only (Control group; 280 patients). All patients were implanted with the PA Sensor and took daily readings from home.

Patients were enrolled regardless of their baseline ejection fraction so that patients with both reduced and preserved systolic function were included. Physicians had access to pulmonary artery pressure information for patients in the Treatment group but not for patients in the Control group.

Following the completion of Randomized Access, patients transitioned to a period of Open Access, during which PA pressures were provided to physicians for patients in both the Treatment and the Control groups. Specifically, physicians continued to have access to the Treatment group's PA pressures in an unchanged manner, whereas access to the Control group's PA pressure was provided for the first time.

Follow-Up Schedule

After right heart catheterization (RHC) and sensor implantation, all patients had follow-up study visits at 1 month, 3 months, 6 months, and every 6 months thereafter until study termination.

Study Endpoints

The primary and secondary endpoints were evaluated after 6 months of patient follow-up. The primary safety endpoints were 1) Freedom from device/system-related complications (DSRC), and 2) Freedom from pressure sensor failures. The primary efficacy endpoint was the rate of HF hospitalizations. All hospitalizations were adjudicated by an independent Clinical Events Committee (CEC) who were blinded to treatment assignment. Secondary endpoints were tested in a hierarchical fashion and included changes in PA pressures, proportion of subjects hospitalized for HF, days alive outside of the hospital for HF, and quality of life.

Because blinded follow-up continued until the last patient completed 6 months of follow-up, the average patient follow-up was much longer (17.6 months) and pre-specified supplementary analyses were conducted on the full duration of follow-up data (Randomized Access).

Patient Demographics and Disposition

575 patients were consented for trial enrollment and underwent right heart catheterization. Of these 575 patients, 25 (4.3%) underwent a right heart catheterization but did not receive an implant primarily because of anatomical/physiological conditions identified during the RHC. Of the 550 randomized patients, 270 were assigned to the Treatment group and 280 to the Control group. The two groups were similar with respect to baseline characteristics (See table below.)

Table 25. Patient Demographics

	Randomized Group		
	Treatment (N=270)	**Control (N=280)**	**p-value[1]**
Age (years)	61.3 ± 12.98 (270)	61.8 ± 12.73 (280)	0.5927
Male	194/270 (71.9%)	205/280 (73.2%)	0.7745
Race (White)	196/270 (72.6%)	205/280 (73.2%)	0.9236
Systolic BP (mmHg)	121.2 ± 22.52 (270)	123.2 ± 21.01 (280)	0.1286
Heart Rate (bpm)	72.4 ± 12.91 (269)	73.0 ± 12.14 (280)	0.4873
BMI	30.5 ± 6.50 (270)	30.9 ± 7.35 (280)	0.6228
BUN (mg/dL)	29.6 ± 17.99 (248)	28.1 ± 16.17 (267)	0.6325
Creatinine (mg/dL)	1.4 ± 0.47 (270)	1.4 ± 0.42 (280)	0.5560
GFR (mL/min/1.73m²)	60.4 ± 22.50 (270)	61.8 ± 23.20 (280)	0.5638
Ejection Fraction (EF>=40%)	62/270 (23.0%)	57/279 (20.4%)	0.5343
Cardiac Output (L/min)	4.5 ± 1.41 (270)	4.6 ± 1.54 (278)	0.5499
Cardiac Index (L/min/m²)	2.1 ± 0.59 (270)	2.2 ± 0.64 (278)	0.4405
PVR	2.9 ± 2.02 (270)	2.7 ± 1.82 (278)	0.4609
PA Wedge Pressure (mmHg)	17.5 ± 7.97 (270)	19.0 ± 8.12 (280)	0.0276
PA Mean Pressure (mmHg)	28.9 ± 9.92 (270)	29.9 ± 10.05 (280)	0.3021
CRT-D/ICD Implant	179/270 (66.3%)	197/280 (70.4%)	0.3145
Ischemic Cardiomyopathy	158/270 (58.5%)	174/280 (62.1%)	0.4327
Hypertension	207/270 (76.7%)	220/280 (78.6%)	0.6100
Hyperlipidemia	204/270 (75.6%)	218/280 (77.9%)	0.5458
Coronary Artery Disease	182/270 (67.4%)	202/280 (72.1%)	0.2290
History of MI	134/270 (49.6%)	137/280 (48.9%)	0.9320
Diabetes Mellitus	130/270 (48.1%)	139/280 (49.6%)	0.7337
AFIB	120/270 (44.4%)	135/280 (48.2%)	0.3932
COPD	76/270 (28.1%)	83/280 (29.6%)	0.7078
ACE/ARB use	205/270 (75.9%)	222/280 (79.3%)	0.3584
Beta Blocker use	243/270 (90.0%)	256/280 (91.4%)	0.6595

1. Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures.

The mean follow-up during Randomized Access was 17.6 months for a total duration of approximately 800 patient years. During the course of Randomized Access, 93 patients in the Treatment group and 110 patients in the Control group exited the study with the primary reason being death.

A total of 347 patients (177 in the Treatment group and 170 in the Control group) completed Randomized Access and entered Open Access. The mean follow-up during Open Access was 13 months for a total duration of approximately 400 patient years. During the course of Open Access, 58 patients in the Treatment group and 43 patients in the Control group exited the study with the primary reason being death.

Primary and Secondary Endpoint Results

Primary Safety Endpoints

The CHAMPION clinical trial met the two primary safety endpoints: (1) Freedom from device/system related complications (DSRC) and (2) Freedom from sensor failure. The protocol pre-specified objective performance criteria (OPC) were that at least 80% of patients were to be free from DSRC and at least 90% were to be free from pressure sensor failure. Of the 575 patients in the safety population, 567 (98.6%) were free from DSRC at 6 months (lower confidence limit 97.3%, $p<0.0001$). This lower limit of 97.3% is greater than the pre-specified OPC of 80% (See first and second tables below.) There were no sensor explants or repeat implants and all sensors were operational at 6 months for a freedom from sensor failure of 100% (lower confidence limit 99.3%, $p<0.0001$). This lower limit of 99.3% is greater than the pre-specified OPC of 90% (See third table below.)

Table 26. Primary Safety Endpoint – Freedom from Device/System Related Complications

Device/System Related Complications[1] (n=575)		Lower 95.2% Confidence Limit[2]	Objective Performance Criterion (OPC)	p-value[3]
Yes	**No**			
8 (1.4%)1	567 (98.6%)	97.3%	80%	p<0.0001

1. DSRCs (8 total) by group: Consented but not randomized (2), Treatment (3), Control (3)
2. Exact 95.2% Clopper-Pearson lower confidence limit
3. p-value from exact test of binomial proportions compared to 80% for all patients

Table 27. Primary Safety Endpoint – Description of Device/System Related Complications

Description	Number of Subjects with Device or System related complication (%) (N = 575)
Hemoptysis	1 (0.2%)
Sensor did not deploy	1 (0.2%)
Transient Ischemic Attack (TIA)	1 (0.2%)
Atypical chest pain	1 (0.2%)
Sepsis → death	1 (0.2%)
Atrial arrhythmia → death	1 (0.2%)
Arterial embolism (upper extremity)	1 (0.2%)
Pulmonary artery (in-situ) thrombus	1 (0.2%)
Total Subjects Experiencing aDSRC	**8 (1.4%[1], 95.2% LCB 97.3%)**

Table 28. Primary Safety Endpoint – Freedom from Pressure Sensor Failures

Pressure Sensor Failures (n=550)[1]		Lower 95.2% Confidence Limit[2]	Objective Performance Criterion (OPC)	p-value[3]
Yes	**No**			
0 (0.0%)	550 (100%)[1]	99.3%	90%	p<0.0001

1. Pressure sensor failure counts by group: Treatment (0), Control (0)
2. Exact 95.2% Clopper-Pearson lower confidence limit
3. p-value from exact test of binomial proportions compared to 90% for all patients

Primary Efficacy Endpoint

The primary efficacy endpoint of the CHAMPION clinical trial was the rate of HF hospitalizations during the first 6 months of Randomized Access. There were 84 HF hospitalizations in the Treatment group compared with 120 HF hospitalizations in the Control group. This difference between the groups represented a 28% reduction in the 6-month rate of HF hospitalization in the Treatment group (0.32 hospitalizations per patient in the Treatment group vs. 0.44 hospitalizations per patient in the Control group, HR 0.72, 95% CI 0.60-0.85, p = 0.0002) (See table below.)

Table 29. Primary Efficacy Endpoint – HF Hospitalization Rates During First Six months of Randomized Access

	Number of HF Hospitalizations	6 Month HF Hospitalization Rate	Hazard Ratio(95% CI) [p-value][1]
Treatment Group (n=270)	84	0.32	0.72 (0.60-0.85) p=0.0002
Control Group (n=280)	120	0.44	

1. p-value and hazard ratio from negative binomial regression model

Secondary Endpoints

The four secondary efficacy endpoints were analyzed hierarchically at six months (See table below.) At baseline, both Treatment and Control patients had similar PA mean pressures. When compared with patients in the Control group, the patients in the Treatment group had greater reduction in mean PA pressure (p=0.0077); were less likely to be hospitalized for heart failure (p=0.0292); spent more days alive outside of the hospital for heart failure (p=0.0280); and reported a better quality of life (Minnesota Living with Heart Failure Questionnaire) (p=0.0236).

Table 30. Secondary Efficacy Endpoints at Six Months

	Treatment	Control	p-value
Change from baseline in mean pulmonary artery pressure, area under the curve (mean mmHg – days)	-155.7 (n=265)	0.32	0.0077[1]
Proportion of patients hospitalized for heart failure(%)	55 (20.4%) (n=270)	80 (28.6%)	0.0292[2]
Days alive outside the hospital for heart failure (mean)	174.4 (n=270)	172.1 (n=280)	0.0280[3]
Minnesota Living with Heart Failure Questionnaire (mean [median])	45.2 [45.0] (n=229)	50.6 [52.0] (n=236)	0.0236[4]

1. p-value from analysis of covariance with baseline pressure as the covariate
2. p-value from Fisher's exact test
3. p-value from Wilcoxon rank sum test after controlling for subject duration in study (i.e., days alive outside the hospital / subject duration x 180)
4. p-value from two-group t-test

Medical Management

Physicians responded to Treatment patients' elevated PA pressures by making medication changes to lower PA pressures in an attempt to reduce the risk for HF hospitalization. Physicians documented all medication changes for all patients and indicated whether the change was made in response to PA pressures or standard of care information. During the six-month follow-up period, physicians made 1113 HF medication changes in the Treatment group and 1061 HF medication changes in the Control group in response to standard of care information. In the Treatment group only, physicians made 1404 HF medication changes in response to PA pressures, primarily through diuretics and vasodilators. This incremental HF management in response to PA pressures using the CardioMEMS™ HF System led to a significant reduction in HF hospitalizations.

Results from the Entire Randomized Access Period

HF Hospitalizations

During the entire Randomized Access period, the rate of HF hospitalizations was 33% lower in the Treatment group than in the Control group (0.46 vs. 0.68 annualized HF hospitalization rates, HR 0.67, 95%CI 0.55-0.80) (see table below). The magnitude of the effect during the entire Randomized Access period was slightly larger than that seen during the 6-month primary endpoint period (33% vs. 28%), indicating durability of the treatment effect. The number needed to treat (NNT) per year to prevent one HF hospitalization was 4. For every 100 patients treated, 23 HF hospitalizations would be prevented per year.

Table 31. HF Hospitalization Rates During Randomized Access

	Number of HF Hospitalizations	Annualized HF Hospitalization Rate	Hazard Ratio[1] (95% CI)	NNT Per Year to Prevent One HF Hospitalization
Treatment Group (n=270)	182	0.46	0.67 (0.55-0.80)	4
Control Group (n=280)	279	0.68		

1. Hazard ratio from Andersen-Gill model.

Mortality

The proportion of patients who died in the Treatment group (18.5%) was smaller than in the Control Group (22.9%) with a relative risk reduction of 20% (HR 0.80, 95% CI 0.55 – 1.15).

Freedom from Death or First HF Hospitalization

The proportion of patients who died or had at least one HF hospitalization in the Treatment group (44.8%) was smaller than in the Control Group (51.8%) with a relative risk reduction of 23% (HR 0.77, 95%, CI 0.60 – 0.98).

All Cause Hospitalizations

All-cause hospitalizations were reduced in the Treatment group (554 in the Treatment group vs. 672 in the Control group, HR 0.84, 95% CI 0.75 – 0.95). The NNT per year to prevent one all-cause hospitalization was 4. For every 100 patients treated, 26 all-cause hospitalizations would be prevented per year.

Death or All Cause Hospitalizations

Death or all-cause hospitalizations were reduced in the Treatment group (604 in the Treatment group vs. 736 in the Control group, HR 0.84, 95% CI 0.76 – 0.94). The NNT per year to prevent one death or all-cause hospitalization was 4. For every 100 patients treated, 29 deaths or all-cause hospitalizations would be prevented per year.

Results from the Open Access Period (Longitudinal Analysis)

In the Open Access period, physicians were given access to PA pressures in the Control group for the first time while access to PA pressures for the Treatment group continued. In the Control group (n=170), new physician access to PA pressures resulted in a 48% reduction in HF hospitalization rates (0.36 vs. 0.68, HR 0.52, 95% CI 0.40-0.69, p<0.0001*). In the Treatment group (n=177), continued physician access to PA pressures resulted in the maintenance of low HF hospitalization rates (0.45 vs. 0.48, HR 0.93, 95% CI 0.70-1.22, p=0.5838*).

To account for potential longitudinal confounders, the change in HF hospitalization rates in the Control group as result of new access to PA pressures was compared to the change in HF hospitalization rates in the Treatment group. The change in HF hospitalization rates in the Control group was significantly greater than in the Treatment group (HR 0.56, 95% CI 0.38-0.83, p=0.0040*), indicating that the significant 48% reduction in HF hospitalization rates observed in the Control group was the result of physician access to PA pressure and not longitudinal effects.

(*P-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Treatment Effects in Women

The CHAMPION study was not powered to show statistical significance for gender, thus a complete determination of the effect of the device in women cannot be made. At the request of the U.S. Food and Drug Administration (FDA), a post-hoc gender analysis was conducted for the CHAMPION study, and the initial finding of a treatment-by-gender interaction for the effect of the CardioMEMS device on the HF hospitalization rate was related to (1) fewer women being in the study and the short duration of follow-up leading to a small number of events in women; and (2) the low HF hospitalization rate in Control women due to an early excess of deaths in women in the Control group, which acted as a competing risk to censor the occurrence of hospitalizations for heart failure.

A further analysis of the treatment-by – gender interaction was performed over the full period of Randomized Access and by incorporating death in the Cox Proportional Hazards. When these limitations and confounding issues were evaluated over the full period, there was neither a qualitative nor quantitative treatment-by-gender interaction and the treatment effect remained positive, independent of gender. However, the analyses conducted do not alleviate the possibility of a diminished treatment effect in women. Given the small number of women enrolled and small number of events observed in women, the true treatment effect in this group remains uncertain. In order to further complement and evaluate the results obtained during the CHAMPION study, the effect of the device in women was studied as part of the post approval study (please refer to results in Long Term Data section.)

The figures below depict the Freedom from HF Hospitalization and Freedom from Death for Men and Women over the Full Randomized Period (Part 1). Figure 10 below depicts the composite endpoint of Freedom from HF Hospitalization or Death for Men and Women over the Full Randomized Period (Part 1). They illustrate the apparent difference in treatment effect by gender. As seen in the first figure below, for HF hospitalizations alone, treatment and control women have similar outcomes. However, as seen in second figure below, control women had an increased early mortality creating a competing risk for HF hospitalizations i.e., fewer control women were alive to have HF hospitalizations. The third figure below examines Freedom from HF Hospitalization or Death and indicates a non-significant trend favoring women in the treatment group.

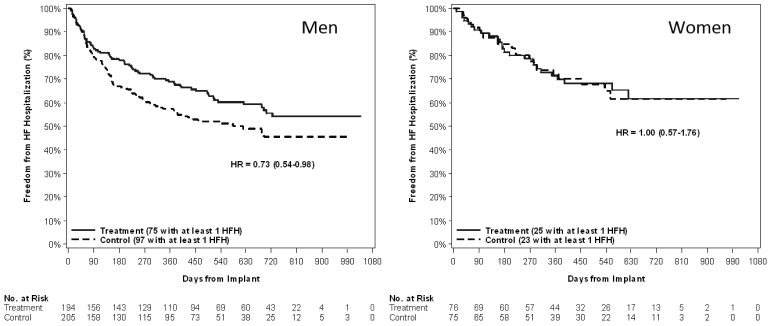


Figure 10. Freedom from HF Hospitalization over the Full Randomized Period (Part 1).

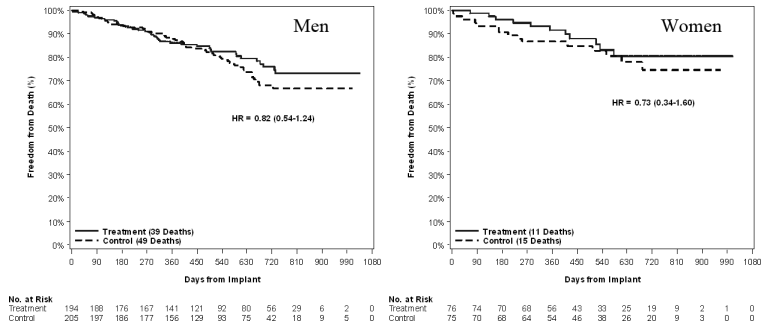


Figure 11. Freedom from Death over the Full Randomized Period (Part 1).

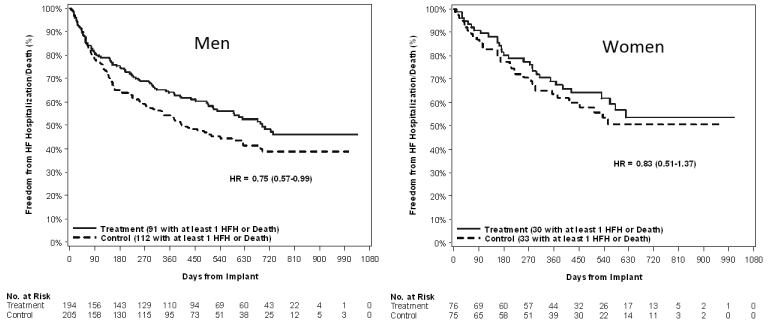


Figure 12. Freedom from HF Hospitalization or Death over the Full Randomized Period (Part 1).

Also performed were an Anderson-Gill Model with Frailty, Anderson Gill Model with Robust Sandwich Estimates (RSE) and Negative Binomial Regression using an endpoint of time to HF hospitalization or death in Part 1 and Part 1 + Part 2. As seen in the two tables below, all the competing risk analyses taking death into account as a competing risk show that there was no evidence of a treatment-by-gender interaction if a p-value of 0.05 is used. However, when analyses for interaction by gender are conducted, a p-value of 0.15 is typically used because the analysis is typically not powered appropriately. When considering a p-value of 0.15, there was some evidence of treatment-by-gender interaction in the competing risk analyses under the following models:

- AG Model with Frailty for Part 1
- NB Regression for Part 1
- AG Model with Robust Sandwich Estimate for Part 1 + Part 2
- GEE NB Regression for Part 1 + Part 2

Table 32. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Part 1			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.113	0.289	0.6968
Cox Model: Endpoint of first HFR hospitalization	-0.330	0.327	0.3131
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.373	0.239	0.1211
AG Model with Frailty: Endpoint of HFR hospitalization	-0.531	0.262	0.0459
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.433	0.316	0.1712
AG Model with RSE: Endpoint of HFR hospitalization	-0.577	0.360	0.1094
NB Regression: Endpoint of HFR hospitalization or Death	-0.412	0.242	0.0896
NB Regression: Endpoint of HFR hospitalization	-0.573	0.191	0.0027

Table 32. Results of treatment by gender interaction using different statistical models

Models	Estimate	SE	p-value
Part 1 + Part 2			
Cox Model: Endpoint of first HFR hospitalization or Death	-0.204	0.249	0.4121*
Cox Model: Endpoint of first HFR hospitalization	-0.427	0.284	0.1331*
AG Model with Frailty: Endpoint of HFR hospitalization or Death	-0.376	0.274	0.1697*
AG Model with Frailty: Endpoint of HFR hospitalization	-0.588	0.271	0.0301*
AG Model with RSE: Endpoint of HFR hospitalization or Death	-0.477	0.274	0.0816*
AG Model with RSE: Endpoint of HFR hospitalization	-0.642	0.313	0.0399*
GEE NB Regression: Endpoint of HFR hospitalization or Death	-0.488	0.283	0.0841*
GEE NB Regression: Endpoint of HFR hospitalization	-0.761	0.319	0.0172*

Table 33. The Treatment vs. Control effects by Gender over Part 1 and over Part 1+ Part 2 under different models

Males	Hazard Ratio	p-value
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.67	0.0007
AG Model with Frailty: Endpoint of HFR hospitalization	0.64	0.0004
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.70	0.0176*
AG Model with Frailty: Endpoint of HFR hospitalization	0.53	<0.0001*
Females		
Part 1 (Treatment vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.99	0.9440
AG Model with Frailty: Endpoint of HFR hospitalization	1.07	0.7584
Part 1 + Part 2 (Former Control vs. Control)		
AG Model with Frailty: Endpoint of HFR hospitalization or Death	0.80	0.4512*
AG Model with Frailty: Endpoint of HFR hospitalization	0.61	0.1482*

(*p-values should be interpreted with caution because the analyses including Part 2 data were not specified before the onset of the study and there are various sources of confounding effects which cannot be separated from the treatment effect.)

Non-Serious Adverse Device Events

There were 17 non-serious adverse device events that occurred over Part 1. There were no additional non-serious adverse device events over Part 2 of the clinical trial. These events were rare and are well known adverse events that occur during right heart catheterization procedures (See table below.)

Table 34. Non-serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	5 (1.9%)	6	7 (2.5%)	11	12 (2.2%)	17	0 (0%)	0
General disorders and administration site conditions	1 (0.4%)	1 (16.7%)	4 (1.4%)	6 (54.5%)	5 (0.9%)	7 (41.2%)	0 (0%)	0 (0%)
Catheter site bleeding	0	0	1	1	1	1	0	0
Catheter site ecchymosis	0	0	1	1	1	1	0	0
Catheter site hematoma	0	0	1	1	1	1	0	0
Chest discomfort	0	0	1	1	1	1	0	0
Chest pain	0	0	1	1	1	1	0	0
Non-cardiac chest pain	1	1	0	0	1	1	0	0
Vessel puncture site pain	0	0	1	1	1	1	0	0

Table 34. Non-serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)			
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Investigations	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)	0 (0%)	0 (0%)
Cardiac monitoring abnormal	1	1	0	0	1	1	0	0
Heart rate irregular	0	0	1	1	1	1	0	0
Serum creatinine increased	1	1	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.7%)	2 (33.3%)	1 (0.4%)	1 (9.1%)	3 (0.5%)	3 (17.6%)	0 (0%)	0 (0%)
Hemoptysis	1	1	1	1	2	2	0	0
Dyspnea	1	1	0	0	1	1	0	0
Cardiac disorders	1 (0.4%)	1 (16.7%)	1 (0.4%)	1 (9.1%)	2 (0.4%)	2 (11.8%)	0 (0%)	0 (0%)
Congestive heart failure	1	1	0	0	1	1	0	0
Ventricular tachycardia	0	0	1	1	1	1	0	0
Nervous system disorders hematoma	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Dizziness	0	0	1	1	1	1	0	0
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (9.1%)	1 (0.2%)	1 (5.9%)	0 (0%)	0 (0%)
Vessel perforation	0	0	1	1	1	1	0	0

Non-Serious Adverse Events Not Related to the Device

Table 35. Non-Serious Adverse Events Not Related to the Device Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)		ALL PATIENTS (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	216 (80.0%)	1229	223 (79.6%)	1135	439 (79.8%)	2364	219 (63.1%)	787
Blood and lymphatic system disorders	27 (10.0%)	37	22 (7.9%)	28	49 (8.9%)	65	13 (3.7%)	16
Cardiac disorders	81 (30.0%)	140	69 (24.6%)	117	150 (27.3%)	257	49 (14.1%)	71
Congenital, familial and genetic disorders	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (0.9%)	3
Ear and labyrinth disorders	6 (2.2%)	6	2 (0.7%)	2	8 (1.5%)	8	2 (0.6%)	2
Endocrine disorders	4 (1.5%)	4	9 (3.2%)	10	13 (2.4%)	14	7 (2.0%)	7
Eye disorders	12 (4.4%)	12	14 (5.0%)	16	26 (4.7%)	28	7 (2.0%)	8
Gastrointestinal disorders	64 (23.7%)	104	60 (21.4%)	96	124 (22.5%)	200	48 (13.8%)	70
General disorders and administration site conditions	64 (23.7%)	102	45 (16.1%)	80	109 (19.8%)	182	50 (14.4%)	62
Hepatobiliary disorders	1 (0.4%)	1	7 (2.5%)	10	8 (1.5%)	11	3 (0.9%)	3
Immune system disorders	4 (1.5%)	4	4 (1.4%)	4	8 (1.5%)	8	4 (1.2%)	4

Table 35. Non-Serious Adverse Events Not Related to the Device Over Part 1 and Part 2

	Part 1						Part 2	
	TREATMENT (270)		CONTROL (280)		ALL PATIENTS (550)		ALL PATIENTS (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Infections and infestations	76 (28.1%)	129	91 (32.5%)	150	167 (30.4%)	279	65 (18.7%)	99
Injury, poisoning and proceduralcomplications	32 (11.9%)	44	32 (11.4%)	37	64 (11.6%)	81	32 (9.2%)	43
Investigations	32 (11.9%)	51	26 (9.3%)	40	58 (10.5%)	91	22 (6.3%)	25
Metabolism and nutrition disorders	66 (24.4%)	116	52 (18.6%)	88	118 (21.5%)	204	37 (10.7%)	53
Musculoskeletal and connectivetissue disorders	49 (18.1%)	75	58 (20.7%)	73	107 (19.5%)	148	56 (16.1%)	70
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	6 (2.2%)	8	9 (3.2%)	9	15 (2.7%)	17	6 (1.7%)	7
Nervous system disorders	61 (22.6%)	86	50 (17.9%)	67	111 (20.2%)	153	47 (13.5%)	56
Psychiatric disorders	34 (12.6%)	46	29 (10.4%)	36	63 (11.5%)	82	25 (7.2%)	31
Renal and urinary disorders	33 (12.2%)	55	35 (12.5%)	45	68 (12.4%)	100	21 (6.1%)	21
Reproductive system and breastdisorders	7 (2.6%)	8	16 (5.7%)	16	23 (4.2%)	24	11 (3.2%)	13
Respiratory, thoracic and mediastinal disorders	68 (25.2%)	97	70 (25.0%)	117	138 (25.1%)	214	47 (13.5%)	66
Skin and subcutaneous tissuedisorders	23 (8.5%)	26	24 (8.6%)	28	47 (8.5%)	54	9 (2.6%)	9
Surgical and medical procedures	17 (6.3%)	21	16 (5.7%)	20	33 (6.0%)	41	16 (4.6%)	19
Vascular disorders	41 (15.2%)	57	39 (13.9%)	46	80 (14.5%)	103	27 (7.8%)	29

Serious Adverse Events Over Part 1 and Part 2

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
All Patients with an Event	**198 (73.3%)**	**797**	**217 (77.5%)**	**956**	**415 (75.5%)**	**1753**	**201 (57.9%)**	**647**
Cardiac disorders	**138 (51.1%)**	**333**	**151 (53.9%)**	**443**	**289 (52.5%)**	**776**	**119 (34.3%)**	**238**
Congestive heart failure	99	204	121	274	220	478	80	140
Heart failure	10	15	13	22	23	37	10	12
Ventricular tachycardia	10	14	12	16	22	30	8	9
Myocardial infarction	7	7	14	14	21	21	9	9
Cardiac pain	13	19	7	22	20	41	0	0
Atrial fibrillation	3	5	10	11	13	16	4	4
Cardiomyopathy	5	6	8	11	13	17	6	7
Cardiopulmonary arrest	3	3	7	7	10	10	3	3
Unstable angina	4	4	5	5	9	9	4	6
Coronary artery disease	5	5	3	3	8	8	4	4

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Ventricular arrhythmia	3	3	5	7	8	10	0	0
Ventricular fibrillation	5	6	2	2	7	8	2	2
Anginal discomfort	1	1	5	8	6	9	2	4
Cardiac arrest	2	2	4	4	6	6	6	6
Ischemic cardiomyopathy	3	4	3	3	6	7	6	7
Atrial flutter	2	2	3	3	5	5	3	3
Cardiogenic shock	2	2	3	3	5	5	3	3
Acute decompensated HF	2	2	1	1	3	3	0	0
ADHF	2	2	0	0	2	2	0	0
Acute coronary syndrome	1	2	1	1	2	3	1	1
Arrhythmia	1	1	1	1	2	2	1	1
Atrial arrhythmia	1	1	1	1	2	2	0	0
Cardiac failure	0	0	2	2	2	2	0	0
Heart disease, unspecified	1	1	1	1	2	2	1	1
Non-ischemic cardiomyopathy	1	1	1	1	2	2	0	0
Sick sinus syndrome	1	1	1	1	2	2	0	0
Angina unstable	0	0	1	1	1	1	0	0
Arrhythmia ventricular	1	1	0	0	1	1	0	0
Arrhythmia ventricular (NOS)	1	1	0	0	1	1	0	0
Atrial tachycardia	0	0	1	1	1	1	0	0
Bradycardia	0	0	1	1	1	1	2	2
Bradycardia-tachycardia syndrome	0	0	1	1	1	1	0	0
Cardiac arrhythmia	1	1	0	0	1	1	1	1
Cardiomegaly	0	0	1	1	1	1	0	0
Cardiorenal syndrome	1	1	0	0	1	1	1	2
Chronic heart failure	1	1	0	0	1	1	0	0
Congestive cardiac failure aggravated	0	0	1	1	1	1	0	0
Coronary artery disease progression	1	1	0	0	1	1	0	0
Coronary atherosclerosis	1	1	0	0	1	1	0	0
Coronary spasm	0	0	1	1	1	1	0	0
Decompensated heart failure	1	1	0	0	1	1	0	0
End stage cardiac failure	0	0	1	1	1	1	0	0
Heart failure, congestive	0	0	1	1	1	1	0	0
Heart valve incompetence	1	1	0	0	1	1	0	0
Intermediate coronary syndrome	0	0	1	1	1	1	0	0
Junctional tachycardia	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Left ventricular dysfunction	1	1	0	0	1	1	0	0
Mitral valve incompetence	1	1	0	0	1	1	1	1
Multi-valvular regurgitation	0	0	1	1	1	1	0	0
Non ST segment elevation myocardial infarction	1	1	0	0	1	1	0	0
Non-sustained ventricular tachycardia	1	1	0	0	1	1	0	0
Pacemaker mediated tachycardia	1	1	0	0	1	1	0	0
Paroxysmal supraventricular tachycardia	1	1	0	0	1	1	0	0
Pericardial disease	1	1	0	0	1	1	0	0
Pericardial effusion	1	1	0	0	1	1	0	0
Pericarditis	0	0	1	1	1	1	1	1
Premature ventricular contractions	0	0	1	1	1	1	0	0
Supraventricular tachycardia	0	0	1	1	1	1	0	0
Sustained ventricular tachycardia	1	1	0	0	1	1	0	0
Tachycardia	0	0	1	1	1	1	0	0
Tricuspid insufficiency	0	0	1	1	1	1	0	0
Ventricular ectopic beats	1	1	0	0	1	1	0	0
Ventricular rhythm	0	0	1	1	1	1	0	0
Wide complex tachycardia	0	0	1	1	1	1	0	0
Wide complex ventricular tachycardia	1	1	0	0	1	1	0	0
Asystole	0	0	0	0	0	0	2	2
Congestive cardiomyopathy	0	0	0	0	0	0	1	1
End stage heart disease	0	0	0	0	0	0	1	1
Hemopericardium	0	0	0	0	0	0	1	1
Palpitation	0	0	0	0	0	0	1	1
Paroxysmal atrial fibrillation	0	0	0	0	0	0	1	1
Polymorphic ventricular tachycardia	0	0	0	0	0	0	1	1
Tachycardia supraventricular	0	0	0	0	0	0	1	1
Infections and infestations	**45 (16.7%)**	**62**	**61 (21.8%)**	**90**	**106 (19.3%)**	**152**	**52 (15.0%)**	**76**
Pneumonia	11	11	15	16	26	27	17	19
Urinary tract infection	5	7	5	6	10	13	5	5
Bronchitis	3	3	5	6	8	9	3	3

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Cellulitis	1	1	6	7	7	8	1	1
Sepsis	3	4	4	4	7	8	7	9
Acute bronchitis	1	1	4	4	5	5	2	2
Bacteremia	1	1	3	5	4	6	2	2
Upper respiratory infection	2	2	2	2	4	4	1	1
Influenza	3	3	0	0	3	3	0	0
Cellulitis of leg	0	0	2	2	2	2	0	0
Cellulitis of legs	0	0	2	2	2	2	0	0
Central line infection	0	0	2	2	2	2	2	2
Endocarditis	0	0	2	2	2	2	0	0
Foot infection	2	3	0	0	2	3	0	0
Gastroenteritis	2	3	0	0	2	3	3	3
Incision site infection	1	3	1	4	2	7	1	1
Infection	0	0	2	2	2	2	1	1
Osteomyelitis	1	1	1	1	2	2	1	1
Pyelonephritis	1	1	1	1	2	2	0	0
Respiratory infection	1	1	1	1	2	2	0	0
Viral gastroenteritis	1	1	1	1	2	2	0	0
Abscess	1	1	0	0	1	1	0	0
Acute diverticulitis	1	1	0	0	1	1	0	0
Acute pyelonephritis	0	0	1	1	1	1	0	0
Bacterial endocarditis	0	0	1	1	1	1	0	0
Bacterial infection	1	1	0	0	1	1	0	0
C.difficile colitis	1	1	0	0	1	1	0	0
Catheter site infection	0	0	1	1	1	1	0	0
Cellulitis of arm	0	0	1	1	1	1	0	0
Cellulitis of hand	1	1	0	0	1	1	0	0
Clostridium difficile infection	1	1	0	0	1	1	0	0
Community acquired pneumonia	0	0	1	1	1	1	1	1
Diverticulitis	1	1	0	0	1	1	2	2
Gastritis viral	0	0	1	1	1	1	0	0
Gastroenteritis adenovirus	1	1	0	0	1	1	0	0
Groin abscess	1	1	0	0	1	1	0	0
HIV-related dementia	0	0	1	1	1	1	0	0
Infection MRSA	0	0	1	1	1	1	0	0
Infection NOS	0	0	1	1	1	1	1	1
Klebsiella bacteremia	1	1	0	0	1	1	0	0
Maxillary sinusitis	1	1	0	0	1	1	0	0
Methicillin-resistant staphylococcal aureus sepsis	0	0	1	1	1	1	0	0
Obstructive pneumonia	1	1	0	0	1	1	0	0
Otitis media	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Pneumonia MRSA	1	1	0	0	1	1	0	0
Prostatitis Escherichia coli	0	0	1	1	1	1	0	0
Purulent bronchitis	0	0	1	1	1	1	0	0
Salmonella infection, unspecified	0	0	1	1	1	1	0	0
Sepsis MRSA	0	0	1	1	1	1	1	2
Septic shock	0	0	1	1	1	1	3	3
Septicemia	0	0	1	1	1	1	0	0
Septicemia staphylococcal	0	0	1	1	1	1	0	0
Serratia infection	0	0	1	1	1	1	0	0
Sinusitis	0	0	1	1	1	1	1	1
Staphylococcal infection	1	1	0	0	1	1	0	0
Urosepsis	1	1	0	0	1	1	0	0
Viral infection	1	1	0	0	1	1	1	1
Viremia	0	0	1	1	1	1	0	0
Wound infection	0	0	1	1	1	1	0	0
Arthritis infective	0	0	0	0	0	0	1	1
Bronchopneumonia	0	0	0	0	0	0	1	1
Clostridium difficile colitis	0	0	0	0	0	0	3	3
Cytomegalovirus viremia	0	0	0	0	0	0	1	1
Febrile cold (excluding flu like illness)	0	0	0	0	0	0	1	1
Febrile infection	0	0	0	0	0	0	1	1
GI infection	0	0	0	0	0	0	1	1
Infection pseudomonas aeruginosa	0	0	0	0	0	0	1	1
MRSA colonization	0	0	0	0	0	0	1	1
MRSA wound infection	0	0	0	0	0	0	1	1
Pneumonia aspergillus	0	0	0	0	0	0	1	1
Septic joint	0	0	0	0	0	0	1	1
Suppurative peritonitis, other	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	**44 (16.3%)**	**58**	**52 (18.6%)**	**85**	**96 (17.5%)**	**143**	**32 (9.2%)**	**40**
Dyspnea	16	23	19	24	35	47	10	10
Respiratory failure	6	6	11	11	17	17	2	2
COPD exacerbation	4	4	11	20	15	24	5	5
Pleural effusion	3	3	3	4	6	7	3	3
Shortness of breath	4	4	2	3	6	7	0	0
Aspiration pneumonia	2	2	1	1	3	3	1	1
Epistaxis	0	0	3	3	3	3	2	2
Pulmonary hypertension	2	3	1	1	3	4	2	2
Respiratory distress	3	3	0	0	3	3	0	0
COPD	1	1	1	1	2	2	0	0
Dyspnea exertional	1	1	1	1	2	2	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Hypoxemia	0	0	2	2	2	2	0	0
Pneumonitis	0	0	2	2	2	2	0	0
Pulmonary edema	0	0	2	2	2	2	1	1
Pulmonary infiltration	0	0	2	2	2	2	1	1
Pulmonary thromboembolism	2	2	0	0	2	2	0	0
Acute respiratory failure	0	0	1	1	1	1	0	0
Apnea	1	1	0	0	1	1	0	0
Asthma	1	1	0	0	1	1	0	0
Asthma aggravated	0	0	1	1	1	1	0	0
Bronchitis asthmatic	0	0	1	1	1	1	0	0
Difficulty breathing	0	0	1	1	1	1	0	0
Dyspnea exacerbated	1	1	0	0	1	1	0	0
Exacerbation of asthma	0	0	1	1	1	1	0	0
Hemoptysis	0	0	1	1	1	1	1	3
Hypoxia	0	0	1	1	1	1	3	3
Productive cough	0	0	1	1	1	1	0	0
Pulmonary mass	1	1	0	0	1	1	0	0
Respiratory arrest	1	2	0	0	1	2	0	0
Chronic obstructive pulmonary disease	0	0	0	0	0	0	3	3
Cough	0	0	0	0	0	0	1	1
Hypoventilation	0	0	0	0	0	0	1	1
Pulmonary embolus	0	0	0	0	0	0	1	1
Tachypnea	0	0	0	0	0	0	1	1
General disorders and administration site conditions	**35 (13.0%)**	**43**	**30 (10.7%)**	**40**	**65 (11.8%)**	**83**	**36 (10.4%)**	**46**
Chest pain	16	20	10	11	26	31	17	26
Weakness	3	5	7	7	10	12	0	0
Chest pain (non-cardiac)	2	2	4	7	6	9	0	0
Fever	1	1	3	3	4	4	2	2
General malaise	3	3	0	0	3	3	1	1
Death	1	1	1	1	2	2	7	7
Pain	2	2	0	0	2	2	0	0
Sudden cardiac death	1	1	1	1	2	2	1	1
Anasarca	0	0	1	1	1	1	0	0
Central line complication	1	2	0	0	1	2	0	0
Chest discomfort	0	0	1	1	1	1	0	0
Chest pain aggravated	0	0	1	1	1	1	0	0
Chronic fatigue	0	0	1	1	1	1	0	0
Edema of lower extremities	1	2	0	0	1	2	2	2
Fatigue	1	1	0	0	1	1	0	0
Fatigue extreme	1	1	0	0	1	1	0	0
Febrile reaction	0	0	1	1	1	1	0	0
Fever of unknown origin	0	0	1	1	1	1	1	1

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Infusion site bleeding	0	0	1	1	1	1	0	0
Multi-organ failure	0	0	1	1	1	1	0	0
Non-cardiac chest pain	0	0	1	1	1	1	1	1
Substernal chest pain	0	0	1	1	1	1	0	0
Sudden death	1	1	0	0	1	1	0	0
Swelling	1	1	0	0	1	1	0	0
Edema	0	0	0	0	0	0	1	1
Malaise	0	0	0	0	0	0	1	1
Organ failure	0	0	0	0	0	0	1	1
Thrombus in catheter	0	0	0	0	0	0	1	1
Ulcer	0	0	0	0	0	0	1	1
Vascular disorders	**33 (12.2%)**	**42**	**27 (9.6%)**	**28**	**60 (10.9%)**	**70**	**15 (4.3%)**	**15**
Hypotension	15	20	13	14	28	34	6	6
Hematoma	2	2	2	2	4	4	0	0
Orthostatic hypotension	2	2	2	2	4	4	0	0
Deep vein thrombosis leg	3	4	0	0	3	4	0	0
Low output state	3	3	0	0	3	3	0	0
Peripheral arterial disease	2	2	1	1	3	3	0	0
Claudication	2	2	0	0	2	2	1	1
DVT of legs	2	2	0	0	2	2	0	0
Aortic stenosis	0	0	1	1	1	1	0	0
Arterial thrombosis (limbs)	1	1	0	0	1	1	0	0
DVT	0	0	1	1	1	1	1	1
Deep vein thrombosis	0	0	1	1	1	1	0	0
Extremity necrosis	0	0	1	1	1	1	0	0
Hemorrhage, unspecified	1	1	0	0	1	1	0	0
Hemorrhagic shock	1	1	0	0	1	1	0	0
Hypertension	0	0	1	1	1	1	1	1
Hypovolemic shock	1	1	0	0	1	1	2	2
Labile blood pressure	0	0	1	1	1	1	0	0
Peripheral vascular disease	0	0	1	1	1	1	0	0
Shock hemorrhagic	0	0	1	1	1	1	0	0
Subclavian artery thrombosis	1	1	0	0	1	1	0	0
Thromboembolic event	0	0	1	1	1	1	0	0
Bleeding	0	0	0	0	0	0	1	1
Cardiovascular collapse	0	0	0	0	0	0	1	1
Hypertensive emergency	0	0	0	0	0	0	1	1
Ischemia	0	0	0	0	0	0	1	1
Nervous system disorders	**29 (10.7%)**	**37**	**28 (10.0%)**	**38**	**57 (10.4%)**	**75**	**27 (7.8%)**	**32**
Syncope	12	15	7	8	19	23	9	13
CVA	2	2	4	4	6	6	2	2

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Stroke	3	3	2	2	5	5	3	3
Presyncope	0	0	3	3	3	3	2	2
Carotid artery stenosis	1	1	1	1	2	2	0	0
Dizziness	1	1	1	1	2	2	1	1
Embolic stroke	1	1	1	1	2	2	0	0
Subarachnoid hemorrhage	1	1	1	1	2	2	0	0
Anoxic encephalopathy	0	0	1	1	1	1	0	0
Ataxia	1	1	0	0	1	1	0	0
Cerebellar infarction	1	1	0	0	1	1	0	0
Cerebral degeneration	1	1	0	0	1	1	0	0
Cerebral infarct	0	0	1	1	1	1	0	0
Cerebrovascular accident	1	1	0	0	1	1	0	0
Disorder brain (chronic)	1	1	0	0	1	1	0	0
Embolic cerebral infarction	0	0	1	1	1	1	0	0
Encephalopathy	0	0	1	1	1	1	1	1
Headache	0	0	1	1	1	1	0	0
Hemorrhagic stroke	0	0	1	1	1	1	0	0
Hepatic encephalopathy	1	1	0	0	1	1	0	0
Hypertensive encephalopathy	0	0	1	1	1	1	0	0
Intracranial hemorrhage	1	1	0	0	1	1	0	0
Ischemic stroke	0	0	1	1	1	1	0	0
Loss of consciousness	1	2	0	0	1	2	1	1
Numbness	0	0	1	2	1	2	0	0
Ophthalmoplegic migraine	0	0	1	1	1	1	0	0
Paresthesia	0	0	1	1	1	1	0	0
Sciatica	1	1	0	0	1	1	0	0
Seizure	1	1	0	0	1	1	0	0
Slurred speech	0	0	1	1	1	1	0	0
Somnolence	1	1	0	0	1	1	0	0
Syncope convulsive	1	1	0	0	1	1	0	0
TIA	0	0	1	1	1	1	2	2
Unresponsive to stimuli	0	0	1	1	1	1	1	1
Vasovagal symptoms	0	0	1	1	1	1	0	0
Weakness left or right side	0	0	1	1	1	1	0	0
Brain injury	0	0	0	0	0	0	1	1
Restless leg syndrome	0	0	0	0	0	0	1	1
Todd’s paralysis	0	0	0	0	0	0	1	1
Transient ischemic attacks	0	0	0	0	0	0	2	2
Vocal cord paralysis	0	0	0	0	0	0	1	1

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Renal and urinary disorders	**33 (12.2%)**	**41**	**24 (8.6%)**	**34**	**57 (10.4%)**	**75**	**20 (5.8%)**	**22**
Acute on chronic renal failure	11	12	9	10	20	22	1	1
Acute renal failure	9	10	7	9	16	19	8	9
Renal insufficiency	9	11	3	4	12	15	5	5
Acute renal insufficiency	0	0	2	2	2	2	0	0
Azotemia	1	1	1	1	2	2	0	0
Chronic kidney disease	1	1	1	1	2	2	0	0
Renal failure	1	1	1	1	2	2	1	1
Acute tubular necrosis	0	0	1	1	1	1	0	0
Chronic renal failure worsened	0	0	1	1	1	1	0	0
End stage renal failure	0	0	1	1	1	1	0	0
Hematuria	1	1	0	0	1	1	0	0
Kidney failure	1	1	0	0	1	1	0	0
Lupus nephritis	0	0	1	1	1	1	0	0
Nephrolithiasis	1	1	0	0	1	1	0	0
Renal artery stenosis	1	1	0	0	1	1	0	0
Renal function abnormal	1	1	0	0	1	1	0	0
Uremia	0	0	1	1	1	1	0	0
Urinary retention	0	0	1	1	1	1	2	2
Chronic renal failure	0	0	0	0	0	0	1	1
Kidney disorder	0	0	0	0	0	0	1	1
Renal disease	0	0	0	0	0	0	1	1
Renal failure acute on chronic	0	0	0	0	0	0	1	1
Gastrointestinal disorders	**24 (8.9%)**	**35**	**31 (11.1%)**	**49**	**55 (10.0%)**	**84**	**36 (10.4%)**	**53**
GI bleed	6	7	7	7	13	14	9	10
Abdominal pain	3	3	5	6	8	9	2	2
Diarrhea	4	4	1	1	5	5	2	2
Nausea	4	4	1	1	5	5	0	0
Gastritis	3	3	1	1	4	4	1	1
Gastrointestinal bleed	0	0	4	6	4	6	6	8
Vomiting	2	2	2	4	4	6	1	1
Constipation	0	0	3	3	3	3	1	1
Pancreatitis	2	2	1	1	3	3	1	1
Ascites	2	2	0	0	2	2	0	0
Dysphagia	1	1	1	1	2	2	2	2
Emesis	2	2	0	0	2	2	0	0
Esophagitis	0	0	2	2	2	2	0	0
Gastroparesis	0	0	2	2	2	2	1	2
Abdominal bloating	1	1	0	0	1	1	0	0
Abdominal wall hematoma	0	0	1	1	1	1	0	0
Chronic epigastric pain	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Dental caries	0	0	1	1	1	1	0	0
Esophageal spasm	1	1	0	0	1	1	0	0
Esophagitis ulcerative	1	1	0	0	1	1	0	0
Gastric polyps	0	0	1	1	1	1	0	0
Gastritis erosive	0	0	1	1	1	1	0	0
Ileus	0	0	1	1	1	1	0	0
Incarcerated umbilical hernia	0	0	1	1	1	1	0	0
Ischemic colitis	0	0	1	1	1	1	1	2
Melena	1	1	0	0	1	1	0	0
Odynophagia	0	0	1	1	1	1	0	0
Rectal bleeding	0	0	1	3	1	3	1	1
Rectal fistula	0	0	1	1	1	1	0	0
Rectal prolapse	0	0	1	1	1	1	0	0
Ventral hernia	1	1	0	0	1	1	2	4
Decay dental	0	0	0	0	0	0	1	1
Duodenitis	0	0	0	0	0	0	1	1
Fecal impaction (causing obstruction)	0	0	0	0	0	0	1	1
Gastric ulcer	0	0	0	0	0	0	1	1
Gastric ulcer haemorrhage	0	0	0	0	0	0	1	1
Gastrointestinal bleed	0	0	0	0	0	0	1	1
Gastrointestinal bleeding	0	0	0	0	0	0	2	2
Hematemesis	0	0	0	0	0	0	1	2
Hematochezia	0	0	0	0	0	0	2	2
Mesenteric ischemia	0	0	0	0	0	0	1	1
Reflux esophagitis	0	0	0	0	0	0	1	1
Right upper quadrant pain	0	0	0	0	0	0	1	1
Small bowel obstruction	0	0	0	0	0	0	1	1
Metabolism and nutrition disorders	**26 (9.6%)**	**33**	**28 (10.0%)**	**38**	**54 (9.8%)**	**71**	**24 (6.9%)**	**30**
Dehydration	7	9	5	5	12	14	8	8
Hyperglycemia	3	4	5	6	8	10	1	1
Hypoglycemia	4	4	2	2	6	6	2	2
Failure to thrive	2	2	3	4	5	6	1	1
Hypokalemia	2	2	3	3	5	5	3	3
Hypovolemia	2	2	3	3	5	5	0	0
Electrolyte imbalance	2	2	2	2	4	4	0	0
Hypervolemia	2	2	2	2	4	4	0	0
Hyponatremia	1	1	3	3	4	4	4	4
Diabetes	2	2	1	1	3	3	0	0
Hyperkalemia	1	1	2	2	3	3	1	1
Diabetes mellitus loss of control	1	1	1	1	2	2	0	0
Anorexia	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Diabetes mellitus	1	1	0	0	1	1	0	0
Hypercalcemia	0	0	1	1	1	1	0	0
Ketoacidosis (diabetic)	0	0	1	1	1	1	0	0
Volume overload	0	0	1	1	1	1	0	0
Diabetes mellitus inadequate control	0	0	0	0	0	0	1	1
Diabetic ketoacidosis	0	0	0	0	0	0	1	1
Gout	0	0	0	0	0	0	1	1
Gout aggravated	0	0	0	0	0	0	2	2
Gout flare	0	0	0	0	0	0	2	3
Hyperosmolar state	0	0	0	0	0	0	1	1
Hypoglycemic attack	0	0	0	0	0	0	1	1
Surgical and medical procedures	**24 (8.9%)**	**28**	**29 (10.4%)**	**34**	**53 (9.6%)**	**62**	**14 (4.0%)**	**15**
Implantable cardioverter defibrillator insertion	4	4	2	2	6	6	0	0
Pacemaker battery replacement	1	1	5	5	6	6	3	3
Cardiac resynchronization therapy	2	2	2	2	4	4	0	0
Heart transplant	1	1	3	3	4	4	2	2
Cardiac catheterization	3	5	0	0	3	5	0	0
Implantable defibrillator replacement	0	0	3	3	3	3	0	0
Amputation	0	0	2	2	2	2	0	0
Cardiac ablation	1	1	1	1	2	2	0	0
Cardiac resynchronization therapy	0	0	2	2	2	2	0	0
Cardioversion	1	1	1	1	2	2	0	0
Cholecystectomy	0	0	2	2	2	2	0	0
Foot surgery	1	1	1	1	2	2	1	1
Inguinal hernia repair	1	1	1	1	2	2	0	0
Abdominal hernia repair	1	1	0	0	1	1	0	0
Brachytherapy	1	1	0	0	1	1	0	0
Cardiac pacemaker revision	1	1	0	0	1	1	0	0
Central line placement	0	0	1	1	1	1	0	0
Colostomy closure	1	1	0	0	1	1	0	0
Epicardial lead placement	1	1	0	0	1	1	1	1
Gallbladder operation	0	0	1	1	1	1	0	0
Gastric bypass	0	0	1	1	1	1	0	0
Implantable defibrillator insertion	1	1	0	0	1	1	1	1
Incisional drainage	1	1	0	0	1	1	0	0
Knee total replacement	0	0	1	1	1	1	0	0
Mitral valve replacement	0	0	1	1	1	1	0	0
Neuroma removal	1	1	0	0	1	1	0	0
Parotidectomy	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Polypectomy	1	1	0	0	1	1	0	0
Stent placement	1	1	0	0	1	1	0	0
Total hip replacement	1	1	0	0	1	1	0	0
Total knee replacement	0	0	1	2	1	2	0	0
Tricuspid valve repair	0	0	1	1	1	1	0	0
Arteriovenous graft	0	0	0	0	0	0	1	1
Catheterization cardiac	0	0	0	0	0	0	2	2
Hospitalization NOS	0	0	0	0	0	0	1	1
Knee surgery NOS	0	0	0	0	0	0	1	1
Left ventricular assist device insertion	0	0	0	0	0	0	1	1
Ventricular assist device insertion	0	0	0	0	0	0	1	1
Injury, poisoning and procedural complications	**18 (6.7%)**	**21**	**16 (5.7%)**	**19**	**34 (6.2%)**	**40**	**15 (4.3%)**	**16**
Lead dislodgement	2	2	2	2	4	4	0	0
Hip fracture	0	0	3	3	3	3	1	1
Bleeding postoperative	1	1	1	1	2	2	0	0
Device malfunction	0	0	2	2	2	2	0	0
Fall	2	2	0	0	2	2	2	2
Head injury	0	0	2	2	2	2	0	0
Lead conductor fracture	2	2	0	0	2	2	0	0
Subdural hematoma	2	2	0	0	2	2	2	2
Accidental overdose	1	1	0	0	1	1	0	0
Ankle fracture	1	1	0	0	1	1	0	0
Cardiac pacemaker malfunction	0	0	1	1	1	1	0	0
Compression fracture	0	0	1	1	1	1	0	0
Contusion	0	0	1	1	1	1	0	0
Device lead damage	0	0	1	1	1	1	0	0
Device lead issue	1	1	0	0	1	1	0	0
Digoxin toxicity	1	1	0	0	1	1	3	3
Femur fracture	0	0	1	1	1	1	0	0
Fracture rib	1	1	0	0	1	1	0	0
Fractured hip	1	1	0	0	1	1	0	0
Fractured nose	1	1	0	0	1	1	0	0
Fractured pelvis NOS	1	1	0	0	1	1	0	0
Hematoma traumatic	1	1	0	0	1	1	0	0
Humerus fracture	0	0	1	1	1	1	0	0
Medical device complication	0	0	1	1	1	1	0	0
Migration of implant	1	1	0	0	1	1	0	0
Motor vehicle accident	1	1	0	0	1	1	0	0
Pneumothorax traumatic	1	1	0	0	1	1	0	0
Skin avulsion injury	0	0	1	1	1	1	0	0
Subdural haemorrhage	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Chemical pneumonitis	0	0	0	0	0	0	1	1
Device complication	0	0	0	0	0	0	5	5
Overdose accidental	0	0	0	0	0	0	1	1
Sciatic nerve injury	0	0	0	0	0	0	1	1
Musculoskeletal and connective tissue disorders	**11 (4.1%)**	**14**	**13 (4.6%)**	**13**	**24 (4.4%)**	**27**	**16 (4.6%)**	**17**
Back pain	0	0	2	2	2	2	1	1
Chest wall pain	1	1	1	1	2	2	0	0
Degenerative joint disease	1	1	1	1	2	2	1	1
Arthritis	1	1	0	0	1	1	1	1
Arthritis single joint	0	0	1	1	1	1	0	0
Back pain aggravated	1	2	0	0	1	2	0	0
Charcot's joint	0	0	1	1	1	1	0	0
Groin pain	0	0	1	1	1	1	0	0
Hemarthrosis involving lower leg	1	1	0	0	1	1	0	0
Lumbar spinal stenosis	0	0	1	1	1	1	0	0
Lupus erythematosus	0	0	1	1	1	1	1	2
Muscle necrosis	1	1	0	0	1	1	0	0
Musculoskeletal chest pain	1	1	0	0	1	1	0	0
Neck pain	1	1	0	0	1	1	1	1
Olecranon bursitis	0	0	1	1	1	1	0	0
Osteoarthritis knee	0	0	1	1	1	1	0	0
Polymyositis	1	1	0	0	1	1	0	0
Pseudogout	0	0	1	1	1	1	0	0
Rheumatoid arthritis	1	1	0	0	1	1	0	0
Rotator cuff tear	1	1	0	0	1	1	1	1
Scleroderma	0	0	1	1	1	1	0	0
Shoulder blade pain	1	1	0	0	1	1	0	0
Spinal column stenosis	1	1	0	0	1	1	0	0
Cervical spondylosis	0	0	0	0	0	0	1	1
Foot pain	0	0	0	0	0	0	1	1
Joint instability	0	0	0	0	0	0	1	1
Knee pain	0	0	0	0	0	0	1	1
Low back pain	0	0	0	0	0	0	1	1
Osteoarthritis knees	0	0	0	0	0	0	1	1
Pain in joint involving lower leg	0	0	0	0	0	0	1	1
Shoulder pain	0	0	0	0	0	0	1	1
Spinal stenosis NOS	0	0	0	0	0	0	1	1
Spondylolisthesis	0	0	0	0	0	0	1	1
Blood and lymphatic system disorders	**13 (4.8%)**	**14**	**10 (3.6%)**	**13**	**23 (4.2%)**	**27**	**14 (4.0%)**	**20**
Anemia	11	12	8	10	19	22	11	12

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Thrombocytopenia	1	1	1	1	2	2	1	1
Anemia microcytic	1	1	0	0	1	1	0	0
Leukocytosis	0	0	1	1	1	1	0	0
Neutropenia	0	0	1	1	1	1	0	0
Anemia aggravated	0	0	0	0	0	0	1	1
Hemolysis	0	0	0	0	0	0	1	5
Neutropenic fever	0	0	0	0	0	0	1	1
Investigations	**10 (3.7%)**	**10**	**5 (1.8%)**	**6**	**15 (2.7%)**	**16**	**3 (0.9%)**	**4**
Serum creatinine increased	2	2	1	2	3	4	0	0
Transplant evaluation	2	2	0	0	2	2	0	0
Anticoagulation drug level above therapeutic	1	1	0	0	1	1	0	0
Blood culture positive	1	1	0	0	1	1	0	0
Blood glucose fluctuation	0	0	1	1	1	1	0	0
INR	0	0	1	1	1	1	0	0
INR increased	1	1	0	0	1	1	0	0
International normalized ratio decreased	0	0	1	1	1	1	0	0
Mediastinoscopy	1	1	0	0	1	1	0	0
Pulmonary arterial pressure increased	1	1	0	0	1	1	1	1
QT interval prolonged	1	1	0	0	1	1	0	0
Ventricular filling pressure increased	0	0	1	1	1	1	0	0
Blood sugar abnormal	0	0	0	0	0	0	1	1
INR decreased	0	0	0	0	0	0	1	1
Urinary output diminished	0	0	0	0	0	0	1	1
Psychiatric disorders	**7 (2.6%)**	**7**	**7 (2.5%)**	**7**	**14 (2.5%)**	**14**	**6 (1.7%)**	**7**
Acute mental status changes	3	3	7	7	10	10	4	4
Agitation	1	1	0	0	1	1	0	0
Delirium toxic	1	1	0	0	1	1	0	0
Panic attack	1	1	0	0	1	1	0	0
Suicidal ideation	1	1	0	0	1	1	0	0
Mental status changes	0	0	0	0	0	0	2	2
Withdrawal syndrome	0	0	0	0	0	0	1	1
Hepatobiliary disorders	**6 (2.2%)**	**8**	**7 (2.5%)**	**8**	**13 (2.4%)**	**16**	**2 (0.6%)**	**3**
Acute cholecystitis	4	4	0	0	4	4	0	0
Cholecystitis	1	1	3	3	4	4	0	0
Cholelithiasis	2	2	0	0	2	2	2	2
Gallstones	0	0	1	1	1	1	1	1
Hepatic fibrosis	0	0	1	2	1	2	0	0
Injury to liver	1	1	0	0	1	1	0	0
Liver disorder	0	0	1	1	1	1	0	0

Table 36. Serious Adverse Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Portal hypertension	0	0	1	1	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (1.9%)**	**7**	**4 (1.4%)**	**5**	**9 (1.6%)**	**12**	**5 (1.4%)**	**5**
Lung cancer	2	2	1	1	3	3	1	1
Large cell lung cancer	0	0	1	1	1	1	0	0
Lung nodule	0	0	1	1	1	1	0	0
Lymphocytic leukemia	0	0	1	1	1	1	0	0
Myelodysplastic syndrome	1	1	0	0	1	1	0	0
Ovarian cancer	1	1	0	0	1	1	0	0
Prostate cancer metastatic	0	0	1	1	1	1	0	0
Skin cancer	1	1	0	0	1	1	0	0
Small cell carcinoma of the lung	1	2	0	0	1	2	0	0
Adenoma	0	0	0	0	0	0	1	1
Breast cancer	0	0	0	0	0	0	1	1
Esophageal cancer	0	0	0	0	0	0	1	1
Lymphoma	0	0	0	0	0	0	1	1
Endocrine disorders	**2 (0.7%)**	**2**	**1 (0.4%)**	**1**	**3 (0.5%)**	**3**	**1 (0.3%)**	**1**
Adrenal insufficiency	1	1	0	0	1	1	0	0
Hypothyroidism	1	1	0	0	1	1	1	1
Myxedema	0	0	1	1	1	1	0	0
Immune system disorders	**2 (0.7%)**	**2**	**1 (0.4%)**	**1**	**3 0.5%)**	**3**	**0 (0.0%)**	**0**
Amyloidosis	1	1	0	0	1	1	0	0
Heart transplant rejection	0	0	1	1	1	1	0	0
Transplant rejection	1	1	0	0	1	1	0	0
Skin and subcutaneous tissue disorders	**0 (0.0%)**	**0**	**3 (1.1%)**	**3**	**3 (0.5%)**	**3**	**3 (0.9%)**	**4**
Diabetic ulcer	0	0	1	1	1	1	0	0
Foot ulcer	0	0	1	1	1	1	0	0
Venous stasis ulcer	0	0	1	1	1	1	0	0
Decubitus ulcer	0	0	0	0	0	0	1	1
Rash	0	0	0	0	0	0	1	2
Skin thinning of	0	0	0	0	0	0	1	1
Benign prostatic hypertrophy	0	0	1	1	1	1	0	0
Reproductive system and breast disorders	**0 (0.0%)**	**0**	**1 (0.4%)**	**1**	**1 (0.2%)**	**1**	**3 (0.9%)**	**3**
Enlarged prostate	0	0	0	0	0	0	1	1
Postmenopausal bleeding	0	0	0	0	0	0	1	1
Vaginal bleeding	0	0	0	0	0	0	1	1

Adverse Device Events

Table 37. Unanticipated or Serious Adverse Device Events Over Part 1 and Part 2

	Part 1						Part 2	
	Treatment (270)		Control (280)		All Patients (550)		All Patients (347)	
	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events
Unanticipated Serious Adverse Device Events	0 (0.0%)	0	1 (0.4%)	1	1 (0.2%)	1	0 (0.0%)	0
Serious Adverse Device Events	2 (0.7%)	2	0 (0.0%)	0	2 (0.4%)	2	0 (0.0%)	0

Unanticipated Serious Adverse Device Events

There was one event during Part 1 reported as a USADE by the investigator but determined not to be serious or device system related by the CEC which reviewed the event on 27 Jun 2009. There were no additional USADEs over Part 2 of the clinical trial.

Serious Adverse Device Events

The two SADEs that occurred during Part 1 were hemoptysis during the implant procedure and an in-situ thrombosis during the right heart catheterization procedure. Both patients were treated and recovered without sequela. There were no additional SADEs over Part 2 of the clinical trial.

Long-Term Data from the CardioMEMS US Post – Approval Study

Summary of the Post-Approval Study Methods

Study Objective

The objective of the CardioMEMS US Post-Approval Study (PAS) was to confirm the safety and effectiveness of the CardioMEMS™ HF System in patients with New York Heart Association (NYHA) Class III heart failure (HF) (a minimum of 35% of the enrolled patients were to be women) who experienced a heart failure hospitalization (HFH) in the previous year.

Study Design

The PAS was a prospective, non-randomized, open-label, multi-center, post-approval study designed to characterize the use of the CardioMEMS HF System as a condition of premarket approval from the U.S. Food and Drug Administration (FDA).

Study Population

Subjects enrolled in the PAS were male and female patients of at least 18 years of age with NYHA Class III heart failure who were hospitalized for HF in the previous 12 months, who met all eligibility criteria, and provided written informed consent. A prerequisite of the study was that at least 35% of the enrolled patients were to be women.

Data Source

Part 11 compliant electronic case report forms (eCRFs) were utilized. Study site staff entered the information required by the protocol onto eCRFs using a validated system that conforms to FDA requirements for electronic data capture. Only authorized site personnel were permitted to enter the CRF data through the electronic data capture (EDC) system deployed by the Sponsor.

Key Study Endpoints

The primary safety endpoints were (1) freedom from device/system-related complications (DSRCs) at 2 years and (2) freedom from pressure sensor failure at 2 years. The primary effectiveness endpoint was the annualized HFH rate at 1 year compared to the annualized HFH rate for 1 year prior to implant.

Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of 1200 subjects were implanted (enrolled) with the CardioMEMS™ sensor at 104 investigational sites in the United States. An additional 14 subjects had attempted implants that were not successful and therefore were not enrolled in the study. These subjects were followed through 30 days per the study protocol before exiting and are included in appropriate analyses. All enrolled subjects were followed for 24 months or until they exited the study. The number of patients who completed 24 months of follow-up was 710 of the 1200 patients enrolled (59.2%).

Study Visits and Length of Follow-up

Following sensor implant, follow-up visits were scheduled at 1 month, 6 months, 12 months, 18 months, and 24 months. All subjects were followed until completion of their 24-month visit or withdrawal from the study. The average length of patient follow-up was 18.7 months.

Summary of the Post-Approval Study Results

Final Safety Findings

The pre-specified performance goals for each of the primary safety endpoints were that at least 80% of the patients were to be free from DSRC and at least 90% of patients were to be free of sensor failure at 24 months. The results (table below) show that freedom from DSRC at 24 months was 99.6% (1209/1214) with a lower confidence bound of 99.0% (0.990), exceeding the pre-specified performance goal of 80%. The results (table below) show that freedom from pressure sensor failure at 24 months was 99.9% with a lower confidence bound of 99.5%, exceeding the pre-specified performance goal of 90%. Both hypotheses had to be met in order to declare the study successful. Both primary safety endpoints were met.

Table 38. Primary Safety Endpoints

Safety Endpoint	Kaplan – Meier Estimate	Proportion	Lower Confidence Limit[3]	p-value[4]
Freedom from DSRC[1]	99.6%	99.6% (1209/1214)	99.0%	p<0.0001
Freedom from Pressure Sensor Failure[2]	99.9%	99.9% (1199/1200)	99.5%	p<0.0001

1. Denominator includes all subjects in the Safety Population.
2. Denominator includes all subjects in the Effectiveness Population.
3. Lower Exact 95% Clopper-Pearson confidence limit.
4. DSRC p-value tests the one-sided binomial proportion is greater than 80% with 95% confidence, and Pressure Sensor Failure p-value tests the one-sided binomial proportion is greater than 90% with 95% confidence.

Final Effectiveness Findings

The primary effectiveness endpoint for this study compares the annualized HFH rate (including recurrent events) at 12 months post-implant with the rate (including recurrent events) 12 months prior to implant. All follow-up through 12 months post – implant or until subject exited the study were included in the analysis. All subjects who were consented and successfully implanted with a pressure sensor–regardless of study completion status– were included in the analysis. The table below denotes the total number of HFHs for all patients in the year prior to implant (1600 HFHs) and for one year after CardioMEMS™ sensor implant (628 HFHs) for all successfully implanted subjects (n=1200). The HFH rate prior to sensor implant was 1.249 HFHs per patient year. After sensor implant, the rate of HFHs was reduced to 0.535 HFHs per patient year. This is a reduction of 57% in HFHs after treatment using the CardioMEMS sensor (p<0.0001).

Table 39. Annualized HFH Rate

	One Year Prior to Implant[1]	**One Year After Implant[2]**	**Ratio (95% CI), p-value[3]**
Number of HFHs	1600	628	0.43 (0.39, 0.47)
One Year HFH Rate[4]	1.249	0.535	P<0.0001

1. Includes all Clinical Events Committee (CEC) adjudicated HFHs with an admission date on the date of implant and through 390 days prior to date of implant.
2. Includes all CEC adjudicated HFHs with an admission date after the implant procedure discharge date through 390 days after the date of implant.
3. Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.
4. HFH Rate is an annualized rate estimated from the Andersen-Gill model.

As noted in the previous section, the CHAMPION trial was not powered to show statistical significance for gender. Because of this, the PAS had a requirement to enroll at least 35% women and a pre-specified effectiveness analysis of annualized HFH rate at one year compared the year prior to implant was evaluated in both women and men. The goal to enroll at least 35% women was met and approximately 38% of patients enrolled in the PAS were women. Note that the rate of HFH at one year in females (0.513) is comparable to that in males (0.553). This is important as it demonstrates that female subjects have a similar response to the use of CardioMEMS as male subjects.

Table 40. Primary Effectiveness by Sex

Sex	One Year Prior to Implant[1] Events (Rate[3])	One Year After Implant[2] Events (Rate[3])	Hazard Ratio (95% CI), p-value[4]	Interaction p-value
Male (N=748)	970 (1.214)	398 (0.553)	0.46 (0.40, 0.52), p<0.0001	0.1587
Female (N=452)	630 (1.319)	230 (0.513)	0.39 (0.33, 0.46), p<0.0001	

1. Includes all CEC adjudicated HFHs with an admission date on the date of implant and through 390 days prior to date of implant.
2. Includes all CEC adjudicated HFHs with an admission date after the implant procedure discharge date through 390 days after the date of implant.
3. HFH Rate is an annualized rate estimated from the Andersen-Gill model.
4. Hazard Ratio, 95% Confidence Interval, and p-value estimated from the Andersen-Gill model with robust sandwich estimates.

Study Strength and Weaknesses

The CardioMEMS US PAS is the first clinical study to produce long-term data on the CardioMEMS™ HF System. The PAS met both of its primary safety endpoints and demonstrated a large reduction (57%) in HFHs at one year. In comparison to the pivotal CHAMPION trial, where freedom from DSRC was 98.6% with a lower 95% confidence limit of 97.3%, the CardioMEMS US PAS freedom from DSRC of 99.6% with a lower confidence limit of 99.0% exceeded the pre-specified performance goal. In the CardioMEMS US PAS, one patient out of 1200 implanted patients (0.1%) had sensor failure, indicating a freedom from pressure sensor failure at 24 months of 99.9%, which is similar to the 100% freedom from sensor failure observed during the CHAMPION trial.

A limitation of the CardioMEMS US PAS single arm design is that there is not a direct comparator provided within the study population for outcomes. However, results from the CardioMEMS US PAS are supported by results from the CHAMPION trial and MEMS-HF study[1] (the first CardioMEMS study outside the US). In the CHAMPION pivotal trial, a 33% relative risk reduction in HFH was observed in treatment patients versus control over an 18-month average follow-up period.[2] Results similar to the CardioMEMS US PAS have been reported from the MEMS-HF study, where a 62% reduction in the HFH rate (HR:0.38, CI:0.31, 0.48; p<0.0001) was observed at 12 months. The CardioMEMS US PAS has demonstrated that the CardioMEMS HF System is safe (99.6% freedom from DSRCs and 99.9% freedom from sensor failure) and effective (57% reduction in HFH), thus demonstrating the long-term safety and efficacy of the CardioMEMS™ HF system.

FCC Statement

This device is approved for wireless transmission under FCC ID number R3PCS-A-000051. This device complies with Part 15 of the FCC Rules. Operation is subject to the following conditions:

- This device may not cause harmful interference.
- This device must accept any interference received, including interference that may cause undesired operation.

Technical Support

For technical support, call 1 877 696 3754.

1. Angermann CE, Assmus, B, Anker, SD, et al. "Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF)". European Journal of Heart Failure. 2020. doi:10.1002/ejhf.1943
2. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, et al. "Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy : complete follow-up results from the CHAMPION randomized trial". Lancet. 2016;387:453-61

St. Jude Medical
387 Technology Circle NW
Atlanta, Georgia 30313
USA

866-240-3335

sjm.com

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