VOLUME 1

SECTION 11: CHRONICLE IHM SUMMARY OF SAFETY AND EFFECTIVENESS

Chronicle IHM Summary of Safety and Effectiveness

Indications

The Chronicle Implantable Hemodynamic Monitor (IHM) System is indicated for the chronic management of patients with moderate to advanced heart failure, who are in NYHA Class III or IV, to reduce hospitalizations for worsening heart failure.

The Model 4328A/B Chronicle Pressure Sensing Leads have application where a Chronicle device is indicated.

Contraindications

There are no known contraindications for the Medtronic Chronicle IHM system.

Device Descriptions and Function

Chronicle IHM System Components

The Chronicle® Implantable Hemodynamic Monitoring (IHM) system consists of the following components:

Chronicle® Implantable Hemodynamic Monitor (IHM): The Chronicle IHM Model 9520B is a multi-programmable, implantable, battery-powered, physiological monitoring and data storage device. The IHM is similar to a pacemaker in physical size and shape but does not provide therapy. The IHM contains all the interface circuitry for recovering and processing the pressure, temperature, activity and EGM sensor signals; memory for data storage; and a telemetry interface for transcutaneous communication.

Chronicle® Pressure Sensing Lead (PSL): The Model 4328A and 4328B Pressure Sensing Leads are transvenous, ventricular, non-pacing leads with absolute pressure sensing capability. The lead provides a unipolar sensing signal from its tip to the titanium case of the IHM for measuring electrical activity (R-waves). It measures pressure and temperature via a sensor located near the tip. The leads are not intended for pacing.

Chronicle® Tracker External Pressure Reference (EPR): The Model 2955HF EPR is an external, pager-sized, battery-powered device carried by the patient to measure barometric pressure. The EPR also contains a magnet, which can be used by the patient to trigger storage of high-resolution data in the IHM during significant events (such as symptoms).

Chronicle® Tracker EPR Base Cable: The Model 5320HF EPR Base Cable provides the means of communication between the EPR and programmer.

Application Software for the Chronicle® Model 9520B: The Model 9982 v2.0 Application Software resides on the Medtronic CareLink Model 2090 Programmer and is used in-clinic to communicate with the IHM and EPR. The programmer Software can change IHM programmable settings and display data such as real-time pressure waveforms and device status.

Medtronic CareLink® Monitor for Chronicle® Systems: The Model 2490F Medtronic CareLink Monitor for Chronicle® Systems ("monitor") is an external battery-powered unit that typically resides in the patient's home. The monitor interrogates both the IHM and EPR and transmits the data via modem and standard telephone line to a private, secure server.

Device Data Management Application: The Model 2491 Device Data Management Application (DDMA) is a server-based software application on the Medtronic CareLink Network. The software receives data transmitted from the monitor and translates it for display on the Network.

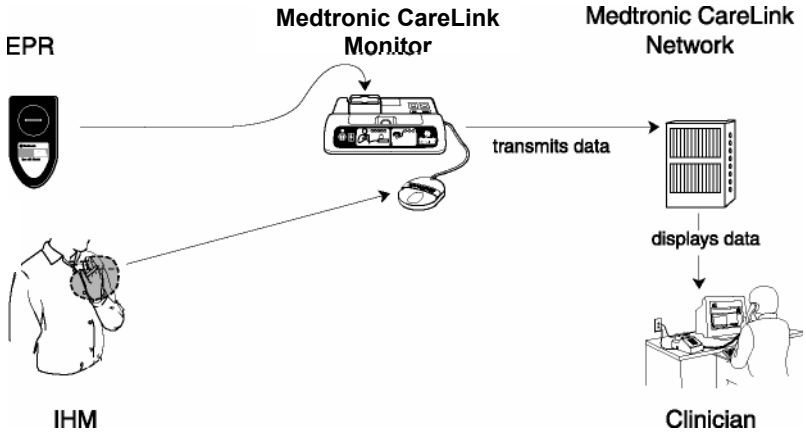
Medtronic CareLink® Network: The Medtronic CareLink Network is a secure, password protected, Web-based application intended for remote viewing of Chronicle data using a standard Internet browser. The data is transmitted to the network directly from the monitor.

Medtronic CareLink® Programmer: The commercially available Model 2090 Medtronic CareLink® Programmer is used to interrogate and program the IHM device.

Remote review of patient data using the Chronicle IHM system

The primary use of the Chronicle IHM system, shown in Figure 1, is for remote patient management[1]. This is accomplished using the following four steps:

Figure 1. Chronicle system components used in remote patient management



1. Patient transmits data to Network

The patient transmits data to the Medtronic CareLink Network as directed by their clinician using a Model 2490F monitor and a standard telephone line. The patient places their EPR into the socket on the monitor, positions the telemetry antenna over their IHM, and presses the power button on the monitor. The monitor automatically interrogates both the IHM and EPR and transmits the data to a private, secure server by means of a built-in modem and a hard-coded telephone access number. This data transfer process is similar to other Medtronic market-released systems.

2. Network prepares data for display

Once the patient data is sent to the Medtronic CareLink Network, the Device Data Management Application (DDMA) Model 2491 and software application

- translates the data from the raw form into a human readable form;
- synchronizes the IHM and EPR pressure data sets in time;
- calculates intracardiac pressure by subtracting the barometric pressure (from the EPR) from the absolute pressure measured by the IHM;
- processes calculated pressure data values for trending and display.

[1] Access to Chronicle data for an in-office or in-hospital follow-up is accomplished by interrogating the IHM and EPR using a Medtronic CareLink programmer. Data can be viewed on the programmer or uploaded to the Medtronic CareLink Network and viewed via an Internet browser.

- stores data on the Medtronic CareLink Network for future review by the clinician.

3. Data is reviewed by clinician

Data is viewed by the clinician via a secure Internet browser connection to the Medtronic CareLink Network. The clinic staff can review chronic pressure data from implant to the current date, review a summary of the most recently transmitted data, add notes to the trend data, and print reports (copies) of this data. The user can then select various menu options to look at the different Trend, Trigger, or Pressure Waveform data that are available.

4. Assess patient status and adjust care as appropriate

To identify clinically meaningful changes in intracardiac pressures, a patient-specific baseline must first be defined. This baseline, termed optivolemia, is the filling pressure required to maintain a balance between minimal congestive signs and symptoms and symptoms of low cardiac output. It is used to make subsequent judgments as to whether the patient is hypervolemic (too wet) or hypovolemic (too dry). If the signs, symptoms, and IHM data suggest that the patient is either hypervolemic or hypovolemic, then an appropriate treatment strategy, based on published ACC/AHA heart failure treatment guidelines, is implemented.

Warnings and Precautions

Model 9520B Chronicle® Implantable Hemodynamic Monitor (IHM):

Device handling

Checking and opening the package – Before opening the sterile package tray, visually check for any signs of damage that might invalidate the sterility of the package contents. Refer to the sterile package opening instructions inside the product box.

If the package is damaged – The device packaging consists of an outer tray and inner tray. Do not use the device or accessories if the outer packaging tray is wet, punctured, opened, or damaged. Return the device to Medtronic because the integrity of the sterile packaging or the device functionality may be compromised. This device is not intended to be resterilized.

Reducing static electricity – The device and lead must be used in an area where measures have been taken to reduce static electricity. These measures include, but are not limited to, grounding of personnel, equipment, and work surface areas.

Handling the pressure sensing lead – Handle the lead with care at all times.

- Do not implant the lead if it is damaged. Return the lead to a Medtronic representative.
- Protect the lead from materials that shed small particles such as lint and dust. Lead insulators attract these particles.
- Do not handle the lead by the sensor capsule or connector pin.
- Handle the lead with sterile surgical gloves that have been rinsed in sterile water or a comparable substance.
- Do not severely bend, kink, or stretch the lead.
- Do not implant the lead if it has been dropped.
- Do not immerse the lead in mineral oil, silicone oil, or any other liquid except blood or sterile water at the time of implant.
- Do not use surgical instruments to grasp the lead.
- Do not force the lead if resistance is encountered during lead passage.

Handling the lead sealing rings – The sealing rings on the connector end of the implantable lead must be protected from damage during insertion and removal from the connector block.

- Before inserting the lead into the device, look into the connector port opening. If the dark colored setscrew is visible, retract the setscrew one turn beyond the point where it disappears from view.
- After pre-implant calibration, loosen the setscrew three turns before removing the lead, to prevent damage to the lead sealing rings.

Dropped pressure sensing lead – Do not implant the pressure sensing lead if it has been dropped after removal from packaging.

Dropped device – Do not implant the device if it has been dropped on a hard surface from a height of 30 cm (12 in) or more after removal from packaging.

For single use only: Do not resterilize and reimplant an explanted device that has been contaminated by contact with body fluids.

Sterilization: Medtronic has sterilized the package contents with ethylene oxide prior to shipment. This device is for single use only and is not intended to be resterilized.

Device Storage

Avoid magnets – To avoid battery depletion, store the device in a clean area away from magnets or kits containing magnets.

Temperature limits – Store and transport the package between –18 °C (0 °F) and +55 °C (131 °F).

Equilibration – Allow the device to reach room temperature before programming or implanting, because rapid temperature changes could affect initial device function and the accuracy of pre-implant calibration.

"Use by" Date – Do not implant the device after the "Use by" date because the battery longevity could be reduced.

Device implant

Accessories – Use this device only with accessories, parts subject to wear, and disposable items that have been tested to technical standards and found safe by an approved testing agency.

Programmer and software – Use the appropriate Medtronic programmer and software to program this device. Programmers from other manufacturers are not compatible with Medtronic devices but will not damage Medtronic devices.

Lead compatibility – Do not use another manufacturer's leads without demonstrated compatibility with Medtronic devices.

Reducing static electricity – The device and pressure sensing lead must be implanted in an environment where measures have been taken to reduce static electricity. The

measures include, but are not limited to, grounding of personnel, equipment, and work surface areas. Preferably, the area in which the lead is implanted should have conductive flooring.

Removing the shorting bar – The shorting bar must be removed from the lead connector prior to implant and in an area where measures have been taken to reduce static electricity. Do not handle the lead connector pin after the shorting bar has been removed. Handle the polyurethane lead body only.

Pre-implant calibration – Perform pre-implant calibration of the pressure sensing lead and device on the sterile surgical table. Move sharp or heavy instruments away from the calibration area to prevent damage to the pressure sensing lead capsule, lead body, or device.

Previously implanted leads – Exercise caution in the placement of the pressure sensing lead in patients with previously implanted ventricular leads. Mechanical contact with a pre-existing lead may cause errors in the cardiac pressure measurements.

Lead evaluation and lead connection

- Do not use ventricular transvenous leads in patients with tricuspid valve disease or a mechanical prosthetic tricuspid valve. Use with caution in patients with a bioprosthetic valve.
- Do not use excessive force or surgical instruments to insert a stylet into a lead.
- Use care when positioning the pressure sensing lead. Avoid known infarcted or thin ventricular wall areas to minimize the occurrence of perforation and dissection.
- Use the correct anchoring sleeve for the lead to immobilize the lead and protect it against damage from ligatures. Use the lead anchoring sleeve to secure the lead lateral to the venous entry site.
- Do not suture directly over the lead body, tie a ligature directly over the lead body, or otherwise create excessive strain at the insertion site. These actions may damage the lead.

Device operation

Battery depletion – Carefully monitor battery longevity. Battery depletion will eventually cause the device to stop functioning.

End of Service (EOS) – Replace the device when the programmer displays an EOL message and a battery voltage of 2.62 volts or less.

Programmers – Use only Medtronic programmers, application software, and accessories to communicate with the device.

Multiple active implanted devices – Do not place or carry the EPR over any other active implanted medical device. The EPR contains a strong magnet that could unintentionally change the operation of the other implant and prevent therapy.

Implanted Chronicle IHM device – Do not carry or wear the EPR over an implanted Chronicle IHM device. This could erase stored data and could result in premature depletion of the Chronicle IHM device battery.

Explant and disposal

Explant and disposal – Explant devices postmortem. In some countries, explanting battery operated implantable devices is mandatory because of environmental concerns; please check your local regulations. In addition, if subjected to incineration or cremation temperatures, the device could explode. Medtronic implantable devices are intended for single use only. Do not resterilize or re-implant explanted devices. Return explanted devices to Medtronic for analysis and disposal. See the back cover for mailing addresses.

Medical therapy hazards

Diathermy – People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and implantable hemodynamic monitors (IHMs), and accompanying leads should not receive diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and/or the need to reprogram or replace the device.

Electrosurgical cautery – Electrosurgical cautery may induce ventricular arrhythmias and fibrillation or may cause device malfunction or damage. If electrosurgical cautery cannot be avoided, observe the following precautions to minimize complications:

- Interrogate the device before the procedure, and turn off data collection until the procedure is completed.
- Keep temporary pacing and defibrillation equipment available.
- Use a bipolar electrocautery system if possible. If unipolar cautery is used, position the ground plate so the current pathway does not pass through or near the device and lead system. The current pathway should be a minimum of 15 cm (6 in) away from the device and lead system.
- Avoid direct contact of the cautery equipment with the implanted device or leads.
- Use short, intermittent, and irregular bursts at the lowest clinically appropriate energy levels.
- Verify proper device operation after electrocautery has been used.

External defibrillation – External defibrillation may damage the implanted device. External defibrillation may also temporarily or permanently damage the myocardium at

the electrode tissue interface. Current flow through the device and lead may be minimized by following these precautions:

- Use the lowest clinically appropriate defibrillation energy.
- Position the defibrillation patches or paddles a minimum of 15 cm (6 in) away from the device.
- Position the defibrillation patches or paddles perpendicular to the device-lead system.

If an external defibrillation is delivered within 15 cm (6 in) of the device, contact a Medtronic representative.

Hyperbaric oxygen therapy (HBOT) – Exposing the device and lead system to pressure levels above 25 psi-absolute could permanently damage the pressure sensor.

Lithotripsy – Lithotripsy may permanently damage the implanted device if it is at the focal point of the lithotripter beam.

Magnetic resonance imaging (MRI) – Do not use magnetic resonance imaging (MRI) on patients who have an implanted device. MRI can induce currents on implanted leads, potentially causing tissue damage and the induction of tachyarrhythmias. MRI may also cause damage to the device.

Radio frequency (RF) ablation – An RF ablation procedure may cause device malfunction or damage. Radio frequency ablation risks may be minimized by observing the following precautions:

- Keep temporary pacing and defibrillation equipment available.
- Position the ground plate so the current pathway does not pass through or near the device and lead system. The current pathway should be a minimum of 15 cm (6 in) away from the device and lead system.
- Avoid direct contact between the ablation catheter and the implanted system.
- Verify implanted device operation after the procedure. Abandon any diagnostic data collected during the procedure.

Therapeutic ultrasound – Exposure of the device to therapeutic ultrasound is not recommended as it may permanently damage the device.

Radiation hazards

Note: Consider the accumulated dose of radiation to the implanted system, from both previous and current exposures, for patients undergoing multiple procedures, such as fluoroscopy or radiation therapy.

Contact your Medtronic representative if you have any questions about the information provided in this section.

Diagnostic radiation and short duration fluoroscopy – The accumulated dose from diagnostic radiation, including chest x-rays, mammograms, computerized axial tomography (CT or CAT) scans, and short duration fluoroscopy, is normally not sufficient to affect the performance of the implanted system.

Device and pressure sensing lead damage from high-dose radiotherapy or long duration fluoroscopy – Do not expose the device or the pressure sensor on the pressure sensing lead to high doses of direct or scattered radiation. An accumulated dose of radiation above 0.5 Gy may affect the performance of the device and pressure sensor; however, the affect may not be immediately apparent. The affect on the performance of the system may be indicated in various ways, including a shift in sensing performance or a clinically noticeable offset in reported pressure and temperature. If an offset occurs, it does not recover over time and should be considered when interpreting the data.

If a patient requires radiation therapy, from any source, do not expose the device or pressure sensor to radiation exceeding an accumulated dose of 0.5 Gy. In cases where a patient requires a long duration fluoroscopic procedure, exposure durations beyond 30 min should be recorded in the patient's medical records for assessment of accumulated exposure. Use appropriate shielding or other measures to limit the radiation exposure to the implanted system. Consider the accumulated dose of radiation to the implanted system from both previous and current exposures for patients undergoing multiple diagnostic procedures, such as fluoroscopy or radiation therapy.

Operational errors associated with photon beam radiotherapy – Exposing the device to direct or scattered neutrons may cause reset of the device, errors in diagnostic data, or loss of diagnostic data. To help prevent device reset due to neutron exposure, deliver radiotherapy treatment using photon beam energies less than or equal to 10 MV. The use of conventional x-ray shielding during radiotherapy does not protect the device from the effects of the neutrons. If photon beam energies exceed 10 MV, Medtronic recommends interrogating the device immediately after radiotherapy treatment. A device reset requires reprogramming of device parameters. Electron beam treatments do not produce this effect.

Home and occupational environments

Barometric pressure in water – Exposing the device-lead system to high pressures such as water at depths beyond 3.05 m (10 ft) can cause a clinically noticeable offset in the reported pressure. This offset may not recover over time and should be considered in

interpreting subsequent data. Re-establish the patient's optivolemic state over the next follow-up period by following the same procedures used at the initial implant of the device.

Cellular phones – This device has been tested using the ANSI/AAMI PC-69 standard to ensure compatibility with cellular phones and other hand-held transmitters with similar power. These transmission technologies represent the majority of cellular telephones used worldwide. The circuitry of this device, when operating under nominal conditions, has been designed to eliminate any significant effects from cellular telephones.

To further minimize the possibility of interaction, observe these cautions:

- Maintain a minimum separation of 15 cm (6 in) between the device and the cellular phone, even if the cellular phone is not on.
- Maintain a minimum separation of 30 cm (12 in) between the device and any antenna transmitting above 3 W.
- Hold the cellular phone to the ear farthest from the device.

Electromagnetic interference (EMI) – Instruct patients to avoid devices that generate strong EMI. Electromagnetic interference may cause device malfunction or damage. The patient should move away from the EMI source or turn off the source because this usually allows the device to return to its normal mode of operation. EMI may be emitted from sources such as:

- high-voltage power lines
- communication equipment such as microwave transmitters, linear power amplifiers, or high-powered amateur transmitters
- commercial electrical equipment such as arc welders, induction furnaces, or resistance welders

Home appliances that are in good working order and properly grounded do not usually produce enough EMI to interfere with device operation. There are reports of temporary disturbances caused by electric hand tools or electric razors used directly over the implant site.

Electronic Article Surveillance (EAS) – Electronic Article Surveillance equipment such as retail theft prevention systems may interact with the implanted device. Advise patients to walk directly through an EAS system, and not remain near an EAS system longer than is necessary.

Static magnetic fields – Patients should avoid equipment or situations where they would be exposed to static magnetic fields greater than 10 gauss or 1 millitesla since it could improperly trigger the device to capture data. Sources of static magnetic fields include, but are not limited to stereo speakers, bingo wands, extractor wands, magnetic badges, or magnetic therapy products.

Models 4328A/B Chronicle® PSL (Pressure Sensing Lead):

Line-powered and battery-powered equipment-- An implanted lead forms a direct current path to the myocardium. During lead implant and testing, use only battery-powered equipment or line-powered equipment specifically designed for this purpose to protect against fibrillation that may be caused by alternating currents. Line-powered equipment used in the vicinity of the patient must be properly grounded. Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

Diathermy -- People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and accompanying leads should not receive diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and the need to reprogram and/or replace the device.

Vessel and tissue damage -- Use care when positioning the lead. Avoid known infarcted or thin ventricular wall areas to minimize the occurrence of perforation and dissection.

Single use -- The lead is for single use only.

Inspecting the sterile package -- Inspect the sterile package with care before opening it.

Contact a Medtronic representative if the seal or package is damaged.

Do not store this product above 40 °C (104 °F).

Do not use the product after its expiration date.

Sterilization -- Medtronic has sterilized the package contents with ethylene oxide before shipment. This lead is for single use only and is not intended to be resterilized.

Reducing static electricity -- The Chronicle device and lead must be used in an area where measures have been taken to reduce static electricity. These measures include, but are not limited to, grounding of personnel, equipment, and work surface areas. Preferably, the area in which the lead is implanted should have conductive flooring.

Removing the shorting bar -- Remove the shorting bar from the lead connector prior to implant, in an area where measures have been taken to reduce static electricity. Do not handle the lead connector pin or the sensor capsule after the shorting bar has been removed. Handle the polyurethane lead body only.

Safe Sheath® Introducer[2]-- The Model 4328B pressure sensing lead is not recommended for use with introducers that have fixed-diameter hemostasis valves, such as the Safe Sheath® introducer.

[2] Safe Sheath is a registered trademark of Pressure Products.

Handling the lead -- Handle the lead with care at all times.

Do not implant the lead if it is damaged. Return the lead to a Medtronic representative.

Protect the lead from materials that shed small particles such as lint and dust. Lead insulators attract these particles.

Do not handle the lead by the sensor capsule or connector pin.

Handle the lead with sterile surgical gloves that have been rinsed in sterile water or a comparable substance.

Do not severely bend, kink, or stretch the lead.

Do not implant the lead if it has been dropped.

Do not immerse the lead in mineral oil, silicone oil, or any other liquid, except blood, at the time of implant.

Do not use surgical instruments to grasp the lead.

Do not force the lead if resistance is encountered during lead passage.

Handling the stylet -- Handle the stylet with care at all times.

Curve the stylet before inserting it into the lead to achieve a curvature at the lead's distal end. Do not use a sharp object to impart a curve to the distal end of the stylet.

Do not use excessive force or surgical instruments when inserting the stylet into the lead.

A stylet cannot be fully inserted into the distal tip of the lead.

Avoid overbending or kinking the stylet.

Use a new stylet when blood or other fluids accumulate on the stylet. Accumulated blood or other fluids may damage the lead or cause difficulty in passing the stylet into the lead.

Necessary hospital equipment -- Keep external defibrillation equipment nearby for immediate use during acute lead system testing, the implant procedure, or whenever arrhythmias are possible or intentionally induced during post-implant testing.

Concurrent devices -- Output pulses, especially from unipolar devices, may adversely affect device sensing capabilities. If a patient requires a separate stimulation device, either permanent or temporary, allow enough space between the leads of the separate systems to avoid interference in the sensing capabilities of the devices.

X-ray radiation -- Exposing the device or pressure sensing lead to high amounts of x-ray radiation (such as with very long fluoroscopy procedures) can cause a clinically noticeable offset in reported pressure and temperature. The effects of x-ray radiation are cumulative over the life of the device. This offset does not recover over time and should be considered when interpreting data subsequent to a procedure. Re-establish the

patient's optivolemic state over the next follow-up period by following the same procedures used at the initial implant of the device.

Susceptibility to therapeutic x-ray -- Exposure to high-energy radiotherapy equipment may damage the device and the pressure sensor on the lead, causing reset of the device, and/or loss of diagnostic data.

Barometric pressure in water-- Exposing the device-lead system to high pressures such as water at depths beyond 3.05m (10 ft) can cause a clinically noticeable offset in the reported pressure. This offset may not recover over time and should be considered in interpreting subsequent data. Re-establish the patient's optivolemic state over the next follow-up period by following the same procedures used at the initial implant of the device.

Hyperbaric oxygen therapy (HBOT) -- Exposing the lead system to pressure levels above 25 psi-absolute could permanently damage the pressure sensor.

Chronic repositioning or removal of a tined lead -- Proceed with extreme caution if a lead must be removed or repositioned. Chronic repositioning or removal of tined transvenous leads may be difficult because of fibrotic tissue development on the lead. In most clinical situations, it is preferable to abandon unused leads in place. Return all removed leads, unused leads, or lead sections to Medtronic for analysis.

Lead removal may result in avulsion of the endocardium, valve, or vein.

Lead junctions may separate, leaving the lead tip and bare wire in the heart or vein.

An abandoned lead should be capped so that the lead does not transmit electrical signals.

Severed leads should have the remaining lead end sealed and the lead body sutured to adjacent tissue.

Alternative Practices and Procedures

The present established therapies for the management of heart failure include pharmacological therapy, cardiac resynchronization therapy, cardiac transplantation, or other surgical procedures. Diagnostic measures to monitor the effectiveness of these interventions, corroborate an event exacerbation, and track the status of heart failure patients over time include Swan-Ganz catheterization, brain natiuretic peptide, and daily weight measurements.

Marketing History

One paragraph removed

Summary of Studies

To validate the performance of the Medtronic Chronicle Implantable Hemodynamic Monitoring system, non-clinical *in vitro* testing and *in vivo* canine testing was performed. The non-clinical and animal testing has demonstrated that the system is safe and performs according to its design intent.

Human clinical trials were performed on the Chronicle system to demonstrate the safe and effective use of the system. The clinical studies conducted have demonstrated that the Chronicle system functions safely and effectively and is appropriate for human use.

In-Vitro Testing

Medtronic thoroughly evaluated the components of the Chronicle system to assess product performance and assure conformance to design specification and reliability intent. All of the *in-vitro* testing demonstrated that the system is safe and performs according to their design intent. This testing is summarized below.

Chronicle Implantable Hemodynamic Monitor (IHM), Model 9520B:

The following tests were completed for the IHM and all passed: Biocompatibility Evaluation, Sterilization Qualification; Product Qualification Report for the , , and Microprocessors; Product Qualification for H0969 Hybrid; Battery Longevity Estimation and Current Drain; Device Qualification for Model 9520B; Electrical Design Verification; Firmware Verification; System Design Verification; Pressure Accuracy; Pressure Accuracy Test report for 4328B; System Test; Connector Qualification; Feedthrough Testing; Package Qualification.

Model 9982 Application Software

Software Verification was completed and passed on the Model 9982 Application Software.

Chronicle Pressure Sensing Lead, Model 4328A/B:

All tests described below are standard tests performed on all leads, except the electrochemical impedance spectroscopy (EIS) test and electrical function tests which are specific to the 4328A lead.

Environmental Conditioning

Two hundred 4328A leads and thirty 4328B leads were subjected to five cycles of ethylene oxide (EtO) sterilization and five cycles of thermal shock (-45C to +70C) prior to undergoing mechanical and electrical testing. No damage or degradation to the test leads was noted following sterilization and thermal shock.

4328A Testing

A minimum of twenty-nine 4328A leads or subassemblies were subjected to the following mechanical tests: tip protector removal, stylet insertion and withdrawal, stylet bottoming/mismatch, stylet perforation, fluid leakage test, introducer compatibility, tip stiffness, visual inspection, composite tensile integrity, connector insertion/withdrawal both wet and dry, composite tensile strength (pin to sleeve, lead body to distal tip and adaptor to feedthrough), and connector flex testing. All samples met requirements. Twenty-two Model 4328A leads or subassemblies were subjected to anchoring sleeve suture test and the lead body flex test. All samples met the requirements. Eighteen samples of 4328A leads were subjected to the composite distal fatigue test (no failures of metallic joints up to 400,000,000 cycles); all of the samples passed.

A minimum of twenty-nine Model 4328A leads were subjected to DC Resistance, IS-1 connector leakage, electrical functional test, and EIS and intermittency testing. All test requirements were met.

4328B Testing

Thirty 4328B leads were subjected to the following mechanical tests: fluid leakage. The adaptor to feedthrough crimp was qualified. All other mechanical testing of the 4328A leads also applies to the 4328B lead as the leads are identical in regards to the testing.

Thirty 4328B leads were subjected to electrical leakage, electrical functional test and intermittency testing. The electrochemical impedance spectroscopy test is not required on the 4328B lead. All test requirements were met.

Biocompatibility Testing

All blood-contacting materials used in the Model 4328A and Model 4328B leads are identical to those used in PMA-approved Medtronic pacing leads. These currently marketed leads have previously been subject to standard biocompatibility evaluations and their materials of construction have been shown to be safe for human implant. All testing performed on previous lead models is applicable to the Model 4328A and 4328B leads.

Sterilization Information

The 100% ethylene oxide (EtO) sterilization process used to sterilize all implantable pulse generators and bradycardia pacing leads has been previously approved. This process is considered an overkill sterilization cycle with twelve logs of reduction. This method is accepted by all major guidelines, including AAMI, ANSI, DSS and ISO/CEN.

All processes used to sterilize a product are validated and qualified according to major guidelines and standards. Validation consists of determining a maximum

allowable bioburden, microbial lethality characteristics and minimum sterilization process specifications. All Medtronic products intended to contact tissue are specified to have a sterility assurance level (SAL) of at least 10-6 (probability of non-sterility).

The procedures used to establish the maintenance and calibration practices for sterilization and aeration equipment are the same as used for other manufacturing equipment.

Package Testing

Package qualification testing was performed on the leads to ensure suitability for their intended purpose. These tests included vehicle stacking, loose load and random vibration, drop tests, and inspection.

Chronicle® Tracker External Pressure Reference (EPR), Model 2955HF

The following tests were completed for the EPR and all passed: Electrical Requirements, Mechanical Requirements, EPR Qualification, EPR Software, EPR Package Qualification.

Medtronic CareLink Monitor for Chronicle Systems, Model 2490F

Testing was performed on Model 2490F monitors to verify that the product conforms to design requirements and intent. All physical and functional requirements were verified. Testing verified that the monitor meets telemetry (monitor connection to IHM), EPR interface (monitor connection to EPR) and telephone connectivity (monitor connection to phone line and transfer protocol) and data management requirements. The monitor firmware was tested against requirements. Finally, testing was performed to verify compliance to environmental standards and requirements such as humidity, electromechanical interference, electro-static discharge mechanical vibration and drop exposure. All test requirements were met.

Device Data Management Application (DDMA) for Chronicle System, Model 2491 on Medtronic CareLink Network

Software sub-system verification and system performance verification testing was performed on the DDMA software. All test requirements were met.

Animal Testing

Three canine studies were performed to evaluate the performance of the Chronicle IHM system with the following objectives.

1. Validate the performance of the Chronicle IHM system including Models 9520 and 4328A.
2. Evaluate the performance of the Chronicle IHM Model 9520B system.
3. Study the stability and performance of the Model 4328B Chronicle PSL.

In all cases, the systems/lead performed as intended.

Clinical Investigation

Medtronic has conducted multiple clinical investigations in support of the development of an implantable hemodynamic monitoring (IHM) system. Two clinical studies, contributing a total of 422 patients' experience are detailed here: the Chronicle Phase I&II study (n=148; IDE #G950062) and the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study (n=274; IDE#G020304).

Phase I&II Study

Clinical evaluation of the Chronicle Phase I&II Study began in August 1998. The purpose of Phase I of the study was to establish the accuracy and reliability of continuous intracardiac pressures monitored by the Chronicle IHM system compared to similar measurements derived from a Swan-Ganz catheter system. Phase II of the study incorporated additional assessment of longer-term safety and performance of the Chronicle system.

The Phase I&II Study used a multi-center, prospective, non-randomized design. In Phase I, with patients serving as their own control, paired right ventricular pressure measurements were taken simultaneously with the Chronicle IHM and a Swan-Ganz catheter. Measurements were obtained at the time of IHM implant and at three-, six-, and 12-month follow-up visits.

Initially, physicians did not use Chronicle data to manage Phase I patients. An interim analysis was performed after 20 Phase I patients were followed for a minimum of six months. The primary effectiveness objectives were tested in 1999 and the results were submitted to FDA demonstrating the Chronicle IHM's effectiveness in measuring right ventricular pressures. Based on the results of the interim analysis, the FDA permitted clinicians to begin using the Chronicle data for patient management.

Phase II eliminated the Swan-Ganz catheterizations. The primary purposes of this phase were to assess safety of the implanted system through three-months and to gain experience

with the clinical utility of the Chronicle IHM. In May 2001, an expansion of Phase II was implemented. The Phase II Expansion allowed for reduced data capture.

Listed below are the specific inclusion and exclusion criteria outlined for entrance into the Chronicle Phase I & II Study:

Patient Selection

Inclusion Criteria:

Patients were eligible for enrollment in the study if they:

- had stable, symptomatic heart failure of greater than three months duration
- were not, in the judgment of the investigator, likely to undergo transplantation within 12 months after implant of the Chronicle IHM.
- were willing and able to participate in all scheduled follow-up visits, including repeated exercise tests
- were of legal age and willing to sign an informed consent

Exclusion Criteria:

Patients were excluded from the study if they:

- had known atrial or ventricular septal defects
- had stenosis of the tricuspid or pulmonic valves
- had a mechanical right heart valve
- had a previously implanted non-Medtronic device in which the transvenous leads were unable to be extracted prior to implanting the Chronicle IHM system*
- had a terminal illness unrelated to their heart failure with a life expectancy of less than 12 months
- had clinical dementia that would prevent them from understanding the use of the Activator and External Pressure Reference
- were female patients that were pregnant or of childbearing potential, and not on a reliable form of contraception as determined by the investigator (due to the multiple X-Rays required under this protocol)
- were participating in another clinical trial that may have confounded the results of this study

* Patients enrolled in Phase II or Phase II Expansion, following approval of , could be enrolled with a pre-existing Medtronic pacemaker or defibrillator

The following section summarizes the Chronicle Phase I & II study primary safety and effectiveness objectives, along with key secondary objectives.

Chronicle Phase I&II Primary Objectives

Effectiveness:

1. The 95% confidence bounds of the accuracy of systolic pressure between the Chronicle IHM system and the Swan-Ganz catheter must be within ± 10 mmHg.
2. The 95% lower confidence bound of the correlation coefficient of systolic pressure must be ≥ 0.90.
3. The 95% confidence bounds of the right ventricular systolic pressure drift rate of the Chronicle IHM system must be within ± 10 mmHg per year.
4. The 95% confidence bounds of the difference in right ventricular systolic pressure measurements between the Chronicle IHM system derived change of resting to provocative testing vs. the Swan-Ganz catheter derived change must be within ± 10 mmHg.
5. The 95% lower bound on reliability of the pressure sensor must be ≥ 90%. Reliability is defined as freedom from any complete failure of the pressure sensor after the system is successfully implanted.

Safety:

1. The lower 95% confidence bound on the freedom from severe device-related adverse events experienced must be ≥ 94% at 3 months.
2. The lower 95% confidence bound on the freedom from device-related complications must be ≥ 85% at 3 months.

Chronicle Phase I & II Key Secondary Objectives

Effectiveness:

1. The correlation coefficient, accuracy, precision and drift rate of diastolic pressure when comparing the Chronicle IHM system and the Swan-Ganz catheter will be described.

2. The correlation coefficient, accuracy, precision and drift rate of the estimated Pulmonary Artery Diastolic (ePAD) pressure when comparing the Chronicle IHM system and the Swan-Ganz catheter will be described.

Phase I Provocative Testing

Patients enrolled in Phase I were expected to complete difficult and rigorous invasive testing at implant, three, six, and 12 months after implant. During these visits, patients underwent a Swan-Ganz catheterization; paired measurements between the Chronicle IHM and the Swan-Ganz catheter were obtained while the patient was at rest (sitting and supine), while performing the Valsalva maneuver, and during a stationary bicycle exercise test. Mean values from 21 cardiac cycles were determined at the end/peak of each provocation. Patient-specific procedures were consistently applied to ensure reproducible position of the Swan-Ganz transducer location at all serial procedures.

Phase II Visits

Patients entering this phase of the study had a Chronicle IHM implanted, but they were not required to undergo Swan-Ganz catheterization at the baseline, three, six, and 12 month follow-up visits. After implant, each patient was followed monthly through four months, every other month from four to twelve months, and then subsequently every three months. An exercise protocol (six-minute hall walk test) and Valsalva maneuvers were performed at four visits during the one year follow-up. Following a change to the Investigational Plan dated May 23, 2002, all patients followed for greater than 12 months entered a long-term follow-up schedule of every six months until market approval.

Demographic Data

Baseline characteristics of the enrolled patients are presented in Table 1 below.

Table 1. Phase I&II Baseline Patient Characteristics

Patient Demographics (n=148)	
Age	56 ± 13 years
Gender	60% male
Baseline Functional Data	
NYHA Class III or IV	77%
LVEF	28 ± 14%
Six-Minute Hall Walk	291 ± 113 meters
Relevant History	
Ischemic Heart Failure Etiology	47%
Systemic Hypertension	52%
Diabetes	41%
Renal Insufficiency	19%
Heart Transplant Candidate	31%
Baseline Medications	
Diuretics	94%
ACE Inhibitors or ARBs	90%
Beta Blockers	62%

Comparable demographics were noted between patients enrolled in Phase I and Phase II with the exception of NYHA Class. Forty-one percent of the Phase I population were NYHA Class II at baseline evaluation, compared to 17% of patients in Phase II. The higher percentage of NYHA Class II patients was attributable to the Phase I protocol requirement of repeated Swan-Ganz catheterizations at baseline, three, six, and 12 months.

Results

The results of the primary objectives and key secondary objectives for the Chronicle Phase I & II study are presented in Table 2. The performance criteria (where applicable) is provided with each objective.

Table 2: Chronicle Phase I & II Study Results

Primary Effectiveness Objectives	Results
The 95% confidence bound on difference between RV systolic pressure measured by the Chronicle IHM system and the Swan-Ganz catheter must be within ± 10 mmHg.	**Objective met.** The 95% C.I. was within ± 10 mmHg during exercise, Valsalva maneuvers, sitting rest, and supine rest over 4 follow-up visits ($p<0.001$ for all). The overall 95% C.I. (-2.5, 0.3) was also within the bounds.
The lower 95% confidence bound on the correlation coefficient between the Chronicle IHM system and a Swan-Ganz catheter in measuring right ventricular systolic pressure is ≥ 0.90.	**Objective Met.** The observed 95% C.I of the correlation coefficient was 0.95 (0.92, 0.97).
The 95% confidence bound on the right ventricular systolic pressure drift rate will be within ± 10 mmHg per year.	**Objective Met:** The mean and 95% C.I. of the observed drift rate was -0.01 (-0.19, 0.18) mmHg per month, or –0.12 (-2.28 , 2.16) mmHg per year ($p<0.0001$)
The two-sided 95% confidence bound on the derived difference in pressure measurements between resting and provocative testing between the Chronicle IHM system and the Swan-Ganz catheter will be within ± 10 mmHg.	**Objective Met:** The observed mean difference between resting and provocative tests between Chronicle IHM and Swan-Ganz catheter (95% C.I.) = -0.4 mmHg (-2.2 , 0.9), $p<0.0001$ for equivalence.
The one-sided, lower 95% confidence bound on the freedom from pressure sensor failures will be ≥ 90%.	The observed percent of sensors without complete failure was 84.1%, with a lower 95% confidence bound of 78.0% **After excluding leads from pre-determined <u>manufacturing lots with process defect:</u>** **Objective Met:** The observed percent of sensors without complete failure was 98.4%, with a lower 95% confidence bound of 94.5%.

Primary Safety Objectives	Results
The lower, one-sided 95% confidence bound on the freedom from severe device-related adverse events experienced with the Chronicle IHM system will be ≥ 94% at three months.	Objective Met. Three serious device-related adverse were recorded in 3 patients, resulting in 97.9% of patients being free from device-related adverse at 3 months. The lower 95% confidence bound was 95.6%
The lower, one-sided 95% confidence bound on the freedom from device-related complications experienced with the Chronicle IHM system will be ≥ 85% at three months.	Objective Met: There were 14 device-related complications observed in 13 patients, resulting in a freedom from device-related complications at 3 months of 90.7 %. The lower 95% confidence bound = 86.0%

Key Secondary Objectives	Results
Compare the accuracy and drift rate of right ventricular diastolic pressure (RVDP) measured by the Chronicle IHM system with that measured by the Swan-Ganz catheter. There were no performance criteria for this objective	▪ Mean difference (95% C.I.) was 1.3 mmHg (0.7, 2.1) ▪ Correlation coefficient (95% C.I.) was 0.87 (0.83 , 0.91) ▪ Drift Rate (95% C.I.) was 0.17 mmHg per month (0.04, 0.03) ▪ Mean difference between resting and provocative tests between Chronicle IHM and Swan-Ganz catheter (95% C.I.) was 0.4 (-0.4 , 1.0)
Compare the accuracy and drift rate of the estimated pulmonary artery diastolic (ePAD) pressure measured by the Chronicle IHM system with that measured by the Swan-Ganz catheter. There were no performance criteria for this objective	▪ Mean difference (95% C.I.) = 1.6 mmHg (0.5, 3.7) ▪ Correlation coefficient (95% C.I.) = 0.84 (0.79 , 0.88) ▪ Drift Rate (95% C.I.) = 0.37 mmHg per month (0.15, 0.58) ▪ Mean difference between resting and provocative tests between Chronicle IHM and Swan-Ganz catheter (95% C.I.) = -1.1 (-2.4 , 0.2)

IHM Guided Patient Management Strategy Development

During Phase II, a group of clinical investigators (

2 lines removed

) developed a patient management strategy to serve as a framework for the consistent application of intracardiac pressures to clinical practice. Since pressure data were continuously available for individual patients, population-based definitions of normal pressure ranges were not applicable to the management of patients implanted with the IHM. Thus, the patient management strategy called for the identification of a patient-specific optivolemic pressure range, reflecting an optimal balance between signs and symptoms of congestion and those of a low cardiac output. Once the patient's optivolemic range was determined, subsequent periodic review of intracardiac pressures resulted in the classification of the patient's volume status as either optivolemic, hypervolemic, or hypovolemic. Based on this classification, the use of specific treatment modalities adapted from the American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult was recommended. This strategy, termed IHM Guided Care, was formalized and incorporated into use during the Phase II portion of the Phase I&II study in March 2001. A summary of the key elements of IHM Guided Care is shown below in Table 3.

Table 3: Summary of IHM Guided Care

State	Pressure (RV Systolic, RV Diastolic, and Estimated PAD)	Treatment Strategy
Hypervolemic	↑	• Adjust medication • Modify dietary restrictions • Consider hospitalization or IV therapy
Optivolemic	↔	• Ongoing management & assessment
Hypovolemic	↓	• Adjust medication • Modify dietary restrictions • Consider hospitalization, fluid administration

The Phase I&II Study confirmed that the IHM system was safe, accurate, and reliable in measuring intracardiac pressures as a physiologic indication of volume status in advanced heart failure patients. The intensive testing during Phase I coupled with the development of a relatively simple approach to defining volume status based on information from the IHM system constituted the basis for a prospective outcome study. The premise of this prospective outcome study was to compare the effectiveness of a novel heart failure

management strategy based on information obtained from the IHM system in reducing heart failure morbidity compared to a strategy based on standard medical care alone.

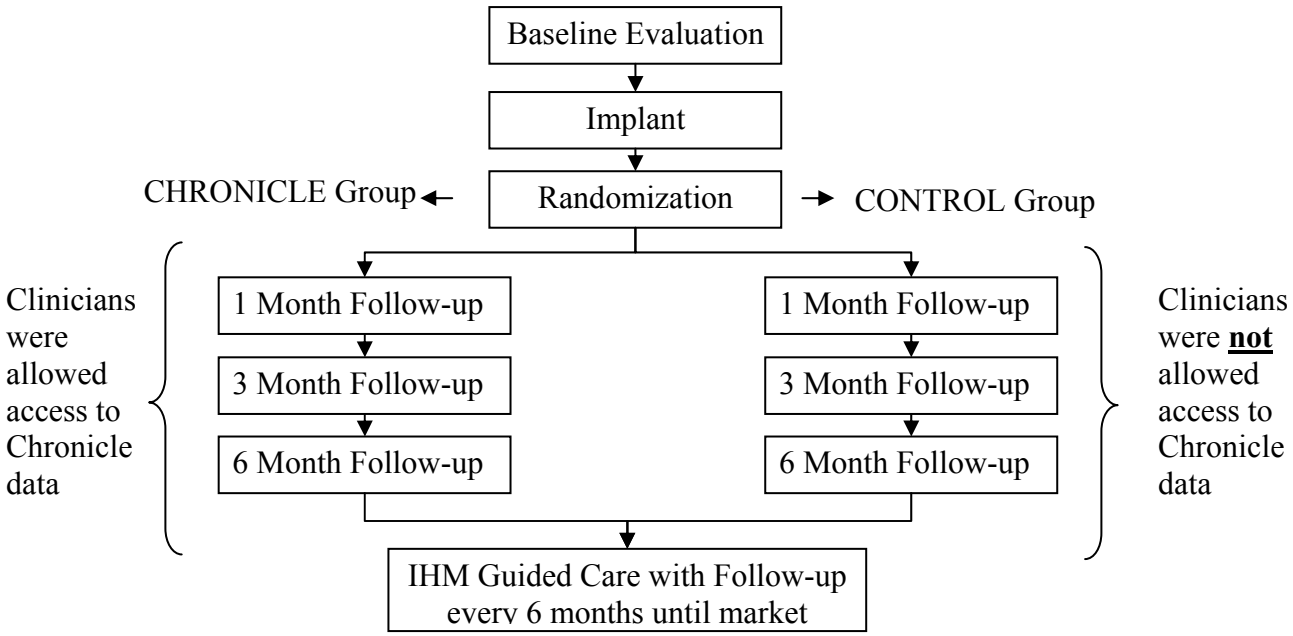
COMPASS-HF Study

Clinical evaluation of the Chronicle Offers Management of Patients with Associated Signs and Symptoms of Heart Failure (COMPASS-HF) study began with the first implant that occurred on March 18, 2003.

COMPASS-HF study was a multi-center, randomized, single-blind, parallel controlled trial designed to evaluate the safety of the Chronicle IHM system and to demonstrate the impact of IHM Guided Care on heart failure-related event rates. Following successful implantation, patients were randomized to either the Total Clinician Access group (CHRONICLE) or Blocked Clinician Access group (CONTROL).

Patients randomized to the CHRONICLE group were treated with standard heart failure medical and device therapy augmented by the use Chronicle data. Patients randomized to the CONTROL group were treated with standard available heart failure medical and device therapy without the use of the Chronicle data until after their six-month clinic visit was completed. After the patient's six-month visit, clinicians were allowed access to the CONTROL patient's trended Chronicle data, including all historical data from the prior six months, on the Chronicle Web site, and patients were seen in the clinic for a protocol-required visit every six months.

Figure 2. COMPASS-HF Study Design



On November 16, 2004 the 274th patient was randomized and enrollment was closed per the investigational plan. Patients continue to be followed in the clinic every six months until the closure of the study.

Primary Safety Objectives

Safety of the Chronicle IHM was evaluated using the following performance criteria:

- The one-sided lower 95% confidence bound on the freedom from system-related complications at six months would be at least 80%.
- The one-sided lower 95% confidence bound on the freedom from pressure sensor failures at six months would be at least 90%.

Primary Effectiveness Objective

For the primary effectiveness endpoint, it was hypothesized that the CHRONICLE group would have a significantly lower rate of combined heart failure-related events (hospitalizations and emergency department and urgent clinic visits requiring intravenous therapy) than the CONTROL group.

Secondary Objectives

A number of secondary objectives, listed below, were evaluated to further characterize the response to IHM Guided Care. There were no pre-specified performance criteria related to the secondary objectives.

- Health care resource utilization
- Days alive out of the hospital
- Composite response endpoint
- Quality of life
- New York Heart Association (NYHA) class
- Six-minute hall walk
- Automated detection of changes in pressure
- Patient survival
- Rate of adverse events

Patient Selection

Inclusion Criteria

Patients were eligible for enrollment in the study if they:

- provided written, informed consent;
- were 18 years of age or older;
- were classified as New York Heart Association (NYHA) Class III or Class IV at baseline evaluation;
- were diagnosed with heart failure and managed with standard medical therapy (such as diuretic, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB), and beta blocker) for at least three months prior to baseline evaluation;
- had at least one heart failure-related hospitalization or at least one heart failure-related emergency department visit necessitating intravenous treatment (e.g. IV diuretic administration) within six months prior to baseline evaluation;
- were willing and able to comply with the protocol, including sending weekly remote monitor transmissions, completing required testing (with the exception of the six-minute hall walk test if the patient was unable to ambulate for reasons other than heart failure) and attend follow-up visits.

Exclusion Criteria

Patients were excluded from the study if they:

- were, in the opinion of the investigator, likely to be transplanted within six months from randomization or would remain hospitalized until transplantation;
- had severe COPD or severe restrictive airway disease (recommend $FEV_1 \leq 1$ liter or $\leq 50\%$ predicted);
- were on continuous positive inotropic therapy;
- had known atrial or ventricular septal defects;
- had mechanical right heart valves;
- had stenotic tricuspid or pulmonic valves;
- had an implanted, incompatible pacemaker or ICD;

- were receiving cardiac resynchronization therapy which had not, in the opinion of the investigator, achieved optimal programming for more than three months;
- had a major cardiovascular event (e.g. myocardial infarction, angioplasty, coronary artery bypass grafting) within three months prior to baseline evaluation;
- had a severe, non-cardiac condition limiting six-month survival;
- had a primary diagnosis of pulmonary arterial hypertension;
- had a serum creatinine ≥ 3.5 mg/dL or were on chronic renal dialysis;
- were enrolled in concurrent studies that might confound the results of this study;
- were of childbearing age without reliable contraceptive measures.

Randomization

Randomization was stratified by center and left ventricular ejection fraction (LVEF), with systolic heart failure defined as an LVEF less than 50% and diastolic heart failure defined as an LVEF greater than or equal to 50%.

Patient Blinding

Since the ability of clinicians to interpret IHM information and implement appropriate medical therapy based on changes in pressure was central to this study, a double-blind design was not possible. As a single-blind study, COMPASS-HF patients were not informed whether their clinician was using data obtained from the Chronicle system to direct their heart failure care. There were three primary areas of concern regarding maintenance of the study blind:

- Potential bias due to the likelihood of increased communication between patients assigned to the CHRONICLE group and their care providers
- Inadvertent unblinding during communication between the patient and the patient's clinician
- Unblinding via use of the programmer during clinic visits prior to the end of the randomized follow-up period

A number of procedures were developed and used to address these concerns and are described below.

Frequency of Communication with Patients

The premise of IHM Guided Care is that when clinicians are able to continuously monitor a patient's hemodynamic data, they will be able to intervene sooner to potentially abort an episode of decompensated heart failure. Since they would have more frequent access to intracardiac pressure information, it was anticipated that clinicians would communicate more frequently with patients randomized to the CHRONICLE group than they would with patients in the CONTROL group.

To ensure balance in the communication between the CHRONICLE and CONTROL groups, surveillance calls to the CONTROL group were incorporated into the study procedures. For each patient in the CONTROL group, the following two surveillance call schedules were used:

- Fixed call schedule – each CONTROL patient received two calls per week for the first 2½ weeks (a total of five calls). The purpose of the fixed schedule was to emulate the regular contact a CHRONICLE patient would have with their clinician during the first few weeks of the study as their optivolemic range was determined.
- Random call schedule – calls were assigned randomly (in frequency and timing) during weeks three through 26 based on a statistical model built from the communication patterns observed during the Phase I and II studies.

Content of Communication with Clinicians

To address the potential for inadvertent unblinding through conversation with study staff, standardized communication scripts were developed for clinician-initiated calls and patient-initiated calls. Consistent with standard methods for assessing heart failure, daily weight and patient symptom data were collected during every patient contact.

Programmer Use During Clinic Visits

The Model 9790 Programmer, which is used with the Chronicle system, is capable of displaying real-time pressure waveforms. During clinic or procedural visits, the programmer might be used for any number of reasons. Because beat-to-beat hemodynamic pressure data are visible on the Programmer's screen, individuals not directly involved in active IHM-enabled patient management were required to operate the programmer to maintain the patient blind.

Application of IHM Guided Care

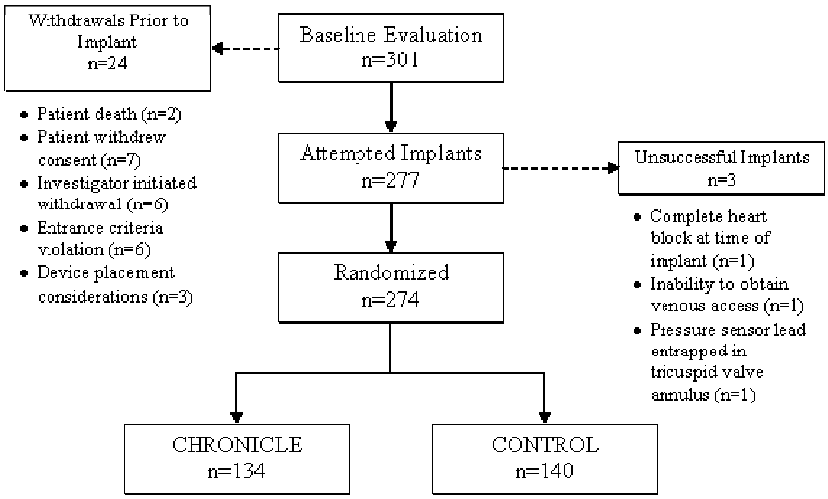
The IHM-guided patient management strategy was developed to assist clinicians with managing their patients' volume status, as described previously under "IHM Guided Care Patient Management Strategy Development." Following implantation, patients were asked to transmit IHM information twice a week using the home monitor. Based on corroborating symptom assessment over the telephone or during a clinic visit, optivolemic ranges were initially set and adjusted as needed to maintain a balance between minimal congestive symptoms and signs and symptoms of low cardiac output.

Once the patient's optivolemic range was defined, it could then be used during each clinician review of the IHM data to determine whether the patient remained optivolemic or had become either hypervolemic (too wet) or hypovolemic (too dry). Treatment strategies adapted from the American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult were offered for each of these hemodynamic states. In summary, the overall goal of IHM Guided Care was to identify and maintain the patient within his or her optivolemic state.

Patient Enrollment and Randomization

Informed consent was obtained and baseline testing was performed in 301 patients. Twenty-four patients were withdrawn prior to Chronicle IHM implant. There were two hundred seventy-seven implant attempts, three of which were unsuccessful. Two hundred seventy-four patients were randomized, including 134 assigned to the CHRONICLE group and 140 to the CONTROL group.

Figure 3: COMPASS-HF Patient Enrollment and Randomization



Total Follow-up Experience

As of January 31, 2006, there were a total of 4,276 patient-months of follow-up with the Chronicle IHM system in 274 randomized patients. Total follow-up per patient ranged from 0.1 to 31.5 months with an average of 15.6 months. In patients originally assigned to the CHRONICLE group, there was a total of 2,100 patient-months of follow-up, ranging from 0.1 to 30.5 months and an average of 15.7 months. In patients originally assigned to the CONTROL group there was a total of 2,176 patient-months of follow-up, ranging from 0.2 to 31.5 months and an average of 15.5 months.

Randomized Follow-up Experience:

There was a total of 1,620 months of randomized follow-up accrued by 274 patients. In the CHRONICLE group, there was a total of 790 randomized months, ranging from 0.1 to 7.7 months and an average of 5.9 months. In the CONTROL group, there was a total of 830 randomized months, ranging from 0.2 to 7.8 months and an average of 5.9 months.

Attrition During the Randomized Follow-up Period

Table 4 provides an overview of the reasons for study exits during randomization. Comparisons between groups showed no significant differences in study exit (p=0.50) or mortality (p=0.61) during randomized follow-up. Survival through six months was verified in four of the five patients that withdrew consent, transferred their care to a different state, or were lost to follow-up. Survival analyses were implemented using the date survival was verified under the intent-to-treat principle.

Table 4. Study Exits During the Randomized Period

Reason for Exit	CHRONICLE	CONTROL	TOTAL
Death	13	11	24
Patient Withdrew Consent	2	0	2
Patient Transferred Care to Different State	1	0	1
Investigator Withdrew Consent	0	1	1
Patient Lost to Follow-up	0	1	1
Total	**16**	**13**	**29**

Patient Demographics

Patients enrolled in COMPASS-HF were advanced heart failure patients with either preserved (≥50%) or depressed (<50%) left ventricular ejection fraction (LVEF). Table 5 summarizes pertinent baseline characteristics for the overall study population.

Table 5. Baseline Demographics

Variable	n	Summary
Age, years (Mean ± SD)	274	58 ± 14
Gender (% male)	274	65%
NYHA (%) Class III Class IV	274	85% 15%
Years since Diagnosis of Heart Failure (Mean ± SD)	274	5.5 ± 5.1
Heart Failure Etiology (% Ischemic)	274	46%
Preserved LV Function, LVEF≥50% (%)	274	26%
Presence of a Concomitant Pacemaker, Implantable Defibrillator or Optimally Programmed Cardiac Resynchronization Device	274	39%
Hospitalizations/ED visits 6 months before Implant (Mean ± SD)	274	2.3 ± 1.8
LV-Ejection Fraction, % (Mean ± SD)	274	32 ± 17
LV-Ejection Fraction, % (Systolic HF patients only, Mean ± SD)	204	24 ± 9
6-Minute Hall Walk, meters (Mean ± SD)	264	236 ± 121

Table 6 summarizes the types of concomitant devices present in patients prior to randomization in number and as a percentage of the entire study cohort (n=274).

Table 6: Devices Prior to Randomization

Device Type	Overall n (%)	CHRONICLE n (%)	CONTROL n (%)
Pacemaker	12 (4%)	7 (5%)	5 (4%)
ICD	48 (18%)	26 (19%)	22 (16%)
CRT	12 (4%)	5 (4%)	7 (5%)
CRT-D	36 (13%)	18 (13%)	18 (13%)
TOTAL	108 (39%)	56 (42%)	52 (37%)

Results – Primary Objectives

The results of the pre-specified primary and secondary objectives for the COMPASS-HF study are presented below in Table 7, Table 8, and Table 11. The performance criteria (where applicable) is provided with each objective.

Table 7: Results of COMPASS-HF Pre-Specified Primary Safety Endpoints

Primary Safety Objectives	Results
Lower one-sided 95% confidence bound of the freedom from Chronicle system-related complications at 6 months is ≥ 80%	24 complications were observed in 23 patients; these events were resolved as follows: ▪ 18 leads repositioned or replaced ▪ 2 systems explanted ▪ 1 lead capped ▪ 1 transesophegeal echocardiogram performed to verify lead migration to the right ventricular apex (to date, sensor performance acceptable) ▪ 1 lead entrapped in the tricuspid valve (lead abandoned) ▪ 1 Chronicle IHM with premature battery depletion (IHM replaced) **Objective Met:** The lower limit of the one-sided 95% confidence bound was 88.7%
Lower one-sided 95% confidence bound of the freedom from pressure sensor failure at 6 months is ≥ 90%	No pressure sensor failures were observed during the study (100% observed freedom rate). **Objective Met:** The lower limit of the one-sided 95% confidence bound was 98.9%

Table 8. Results of COMPASS-HF Pre-Specified Primary Effectiveness Endpoint

Primary Effectiveness Objectives	Results
The CHRONICLE group will have a significantly lower rate of heart failure related hospital equivalents than the CONTROL group through 6 months. Note: Heart Failure Related Hospital Equivalents (HE), included heart failure (HF) related hospitalizations, HF related emergency department and urgent clinic visits requiring intravenous intervention. HEs were adjudicated by an independent, blinded Events Committee.	▪ There were 84 observed heart failure-related HE in 44 CHRONICLE patients (33% of the CHRONICLE patients affected) ▪ There were 113 observed heart failure-related HE in 60 CONTROL group patients (43% of the CONTROL patients were affected) **Objective Not Met:** This observation represents a 21% reduction in the rate of HF-related hospital equivalents, which did not reach statistical significance (p=0.33), using the negative binomial regression methodology.

The data gathered for the primary effectiveness endpoint demonstrated that:

- Heart failure hospitalizations constituted 87% of all events contributing to the composite endpoint in both groups;
- Emergency department and urgent heart failure clinic visits constituted a small proportion of the overall events (13%); and
- there was no observed increase in emergency department or urgent heart failure clinic visits requiring IV therapy as a result of IHM Guided Care.

The majority of heart failure events observed in the COMPASS-HF study were hospitalizations. The relative risk of a heart failure-related hospitalization is a traditional endpoint used as a measure of morbidity in heart failure studies. This analysis was performed on the COMPASS-HF dataset to further assess the impact of IHM Guided Care on morbidity, and these data are presented in the Post Hoc Analyses Section.

Factors Influencing the Primary Effectiveness Objective

The following considerations are relevant in examining factors that may have affected the pre-specified effectiveness outcome of the study:

Impact of Frequent Communication on Heart Failure Event Rate

The premise of IHM Guided Care is that when clinicians are able to continuously monitor hemodynamic data, they might be able to intervene sooner and potentially abort an episode of decompensated heart failure. Because they have frequent access to intracardiac pressure information, it was anticipated that clinicians would communicate more frequently with patients randomized to the CHRONICLE group than they would with patients in the CONTROL group. To ensure balanced communication between clinicians and patients in both groups, random and scheduled surveillance calls to patients in the CONTROL group were incorporated into the study procedures as described previously in the section entitled, Patient Blinding above. The final observed call rates were compared when all patients had reached the end of the randomized period. Table 9 provides the details of these observations.

Table 9. Comparison of Observed Call Rates During Randomized Period

Call Type	Group	Mean Call Rate (Calls/Patient)	p-value
Clinician-Initiated	CHRONICLE (n=134)	21.6	0.88
	CONTROL (n=140)	21.8	
Patient-Initiated	CHRONICLE (n=134)	3.1	0.51
	CONTROL (n=140)	2.9	
Overall Call Rate	CHRONICLE (n=134)	24.7	0.94
	CONTROL (n=140)	24.7	

Clinician-initiated call rates were not statistically different, indicating that the CHRONICLE and CONTROL groups were contacted with a similar frequency. It was also observed that patient-initiated calls were also similar for the groups, as was the overall communication rate.

This strategy was successful, as confirmed by a survey implemented at the end of the six-month randomized follow-up period, when 63% of the patients in the CONTROL group and 75% in the CHRONICLE group thought they were being managed based on the information from the IHM.

Since frequent patient contact with heart failure management teams has previously been shown to reduce hospitalizations, it is likely that this increased level of interaction, which is not usually seen in most heart failure programs, contributed to the relatively low average event rate observed in the CONTROL arm (0.85 vs. the hypothesized 1.2 events per six months, and vs. 1.9 in the six months prior to enrollment in COMPASS-HF).

Event Rate and Associated Power

During the design of the COMPASS-HF study, several assumptions were made about the CONTROL group and their rate of healthcare utilization (in terms hospital equivalents as described previously) during the randomized phase of the study. As mentioned, it was hypothesized that these patients would experience an event rate of 1.2 events per six months with a variance equal to the mean rate (i.e. a Poisson distribution). These assumptions contributed to an estimated power of 80% for the study's primary effectiveness endpoint.

As observed, the 140 patients in the CONTROL group experienced a mean event rate of 0.85 over the randomized period, with a higher variance than was assumed. This departure from the original event rate assumption resulted in a loss of power, which may have hindered the ability of the trial to meet its primary endpoint. Specifically, the study realized a power of 68% to detect a 30% reduction in the primary effectiveness objective event rate. Table 10 summarizes these results.

Table 10. Event Rate and Associated Power

	Study Design Assumptions	Observed Results
CONTROL group: Average Event Rate	1.2	0.85
CONTROL group: Variance	1.2	2.3
Power	80%	68%

Therefore, the combined effect of the rigorous blinding policy that resulted in a markedly lower than anticipated CONTROL event rate, and the greater than anticipated variability in the incidence of heart failure events resulted in an overall loss of power (68% actual versus 80% hypothesized), which likely hindered the ability of the trial to meet its primary endpoint.

Results – Secondary Objectives

Several secondary objectives were planned and investigated in the COMPASS-HF study. None of the specified secondary objectives had associated performance criteria. The results of these secondary objectives are summarized below in Table 11.

Table 11. Results of COMPASS-HF Secondary Objectives

Secondary Objectives	Results
Health Care Utilization: To further characterize the health care utilization between the CHRONICLE and CONTROL groups	Overall the CHRONICLE group experienced: • A significant reduction (**p=0.04**) in the cumulative days in the hospital for heart failure. o A 41% reduction in the proportion of patients with 1 to <10 days of heart failure hospitalization o A 54% reduction in the proportion of patients with 10 to <20 days of heart failure hospitalization o A 22% increase in the proportion of patients that were free of a heart failure-related hospitalization
Days Alive out of the Hospital: To characterize hospitalization-free survival out to 6 months in patients receiving the Chronicle system	The mean days alive out of the hospital for the CHRONICLE group over the six-month randomized period was 171, compared to 173 days for the CONTROL group. This result was not significant.
Composite Response Endpoint: To summarize the composite response endpoint for patients in both the CHRONICLE and CONTROL groups with respect to either "worsened", "improved" or "unchanged" heart failure status	Overall, patients in the CHRONICLE group performed better than in the CONTROL group, although not statistically significant (p=0.11).

Secondary Objectives	Results
Quality of Life: To characterize quality of life between the CHRONICLE group and the CONTROL group using the Minnesota Living with Heart Failure Questionnaire	• The median change in quality of life (QOL) score from Baseline to 3-months post implant was -10.0 in the CHRONICLE group compared to -6.0 in the CONTROL group (a reduction in score reflects an improved QOL). • From Baseline to 6-months, the median change in QOL score was -11.0 in the CHRONICLE group compared to -8.0 in the CONTROL group. Comparison of the changes in QOL score between the groups was not significant (p=0.59) across all times.
NYHA Class: To summarize and compare the functional clinical status of patients in the CHRONICLE and CONTROL groups by NYHA Class.	• At Baseline, 84% of the CHRONICLE group patients considered NYHA Class III (16% were Class IV). This compared to 87% Class III and 13% Class IV in the CONTROL group • At six-months, the CHRONICLE group was 6% Class I, 35% Class II, 54% Class III, and 5% Class IV. The CONTROL group was comparable at 9%, 25%, 57%, and 8%, respectively No difference was observed in the change in functional status between the groups (p=0.36)
Six-Minute Hall Walk: To characterize sub-maximal exercise tolerance as measured by the six-minute hall walk test between the CHRONICLE group and the CONTROL group	• The mean change in the distance walked between Baseline and 3-months was an increase of 9.0 meters in the CHRONICLE group, compared to a reduction of 3.5 meters in the CONTROL group • The mean change in the distance walked between Baseline and 6-months was an increase of 6.2 meters in the CHRONICLE group, compared to a reduction of 8.2 meters in the CONTROL group While these results favored the CHRONICLE group, the difference between the groups was not significant (p=0.31)

Secondary Objectives	Results
Automated Detection of Changes in Pressure: To evaluate the accuracy of an automated algorithm to detect changes in pressures that may be indicative of impending heart failure decompensation.	In the analysis of CONTROL patient data, the sensitivity of the automated detection algorithm ranged from 77-82% depending on the pressure parameter used. The specificity ranged from 74-78%. Similarly, the analysis of all patient data demonstrated 80-83% sensitivity and 74-79% specificity, depending on the pressure parameter used.
Patient Survival: To characterize survival out to 6 months in patients receiving the Chronicle system	Comparisons between the CHRONICLE and CONTROL groups showed no significant differences in mortality (p=0.61) during the randomized follow-up period.

Physiologic Basis for Hemodynamic Monitoring and its Clinical Applications

In the acute setting, evidence to date clearly underscores the strong relationship between changes in underlying physiology and clinical signs and symptoms of decompensated heart failure. The Chronicle IHM system, for the first time, provides insight into changes in ambulatory hemodynamics and their relationship to impending worsening heart failure.

The following topics are discussed in this section:

- Relationship between dynamic intracardiac pressures and heart failure events
- Medication interventions related to changes in dynamic intracardiac pressures
- Long term effect of IHM Guided Care

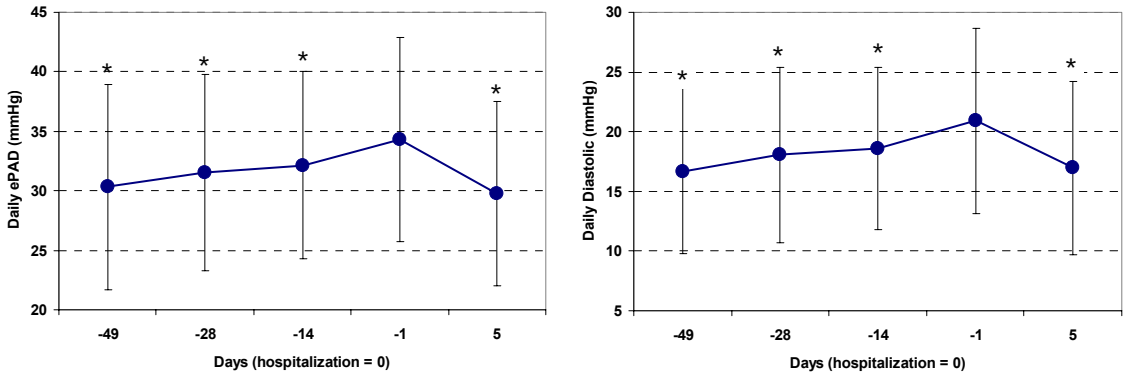
Relationship Between Dynamic Intracardiac Pressures and Heart Failure Events

Time Course of Intracardiac Pressures and Heart Failure Events

Previous studies have documented the relationship between volume overload events and increased filling pressures as measured in the acute setting (when patients present with clinical symptoms of congestion and decompensation). The intent of this analysis is to evaluate the relationship between volume overload events and pressures preceding the onset of clinical symptoms for such events. Therefore, only hypervolemic events were used in this analysis.

Figure 4 below illustrates the changes in daily ePAD and RVDP in the period preceding and immediately following a heart failure hospital equivalent event for volume overload for patients in the CHRONICLE and CONTROL groups.

Figure 4. Daily ePAD and RVDP Measurements in the Days Preceding Hospitalization and Five Days Following Admission



Note: "-1 Day" above is defined as event peak; "+5 Day" is defined as recovery[3]
* $p < 0.01$ comparing pressure values with event peak (-1 Day)

As the figure illustrates, there was a significant and consistent rise in intracardiac pressures starting at 49 days prior to admission for a hypervolemic event (i.e. hospitalization, emergency department visit, or urgent clinic visit requiring IV therapy for heart failure). Pairwise

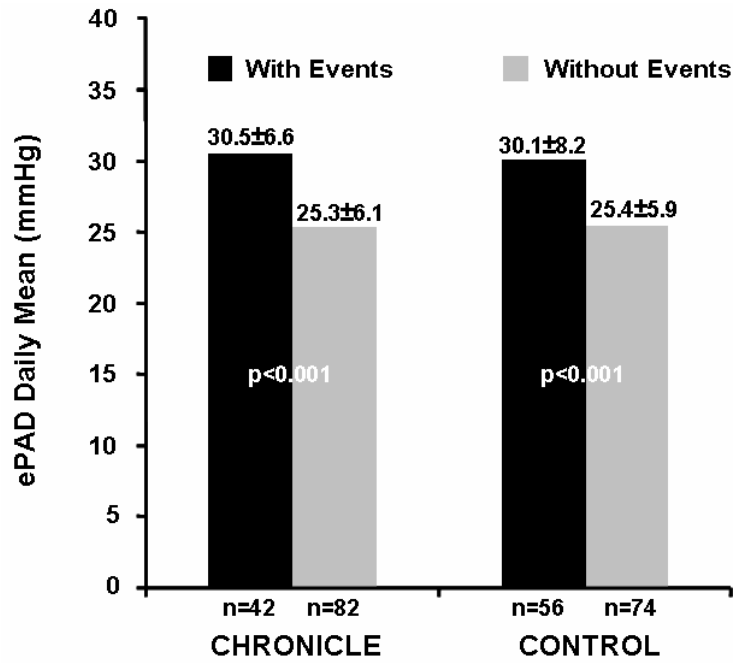
[3] Adamson PB, Magalski A, Braunschweig F, Ongoing Right Ventricular Hemodynamics in Heart Failure: Clinical Value of Measurements Derived from an Implantable Monitoring System. *JACC* 2003; 41:565-571.

comparisons between average pressures at 49, 28, and 14 days before admission and 5 days after admission were significantly lower than peak pressure ($p < 0.01$). The pressures-over-time curves trended upward (i.e. the slope was positive, $p<0.01$) confirming the significance of the sustained rise in pressures preceding hypervolemic events.

Magnitude of Intracardiac Pressures and Heart Failure-Related Events

Regardless of randomization assignment, patients who experienced heart failure events recorded significantly higher average ePAD values than those patients who did not experience heart failure events, suggesting that higher average filling pressures are associated with greater heart failure morbidity.

Figure 5. Intra-cardiac Pressures in Patients With and Without HF Events

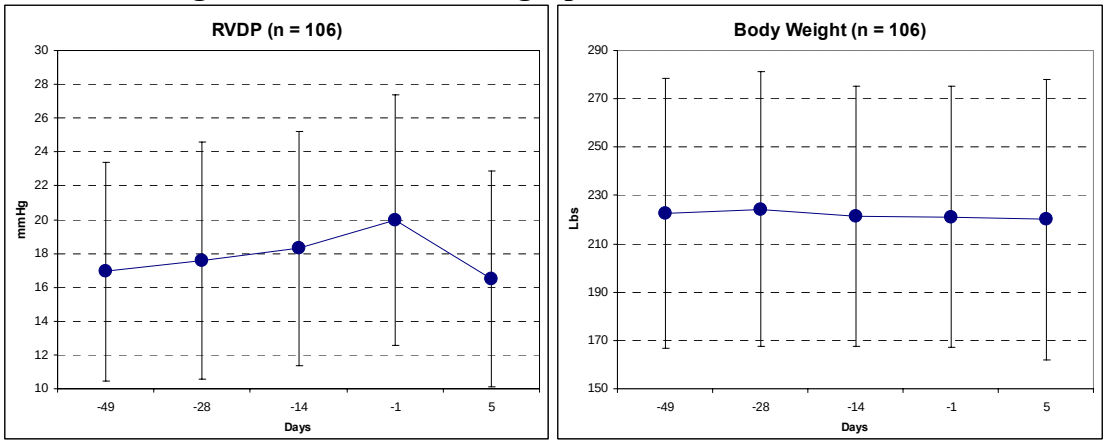


Intracardiac Pressure and Daily Weight Observations

In both the CHRONICLE and CONTROL groups, there is a consistent increase in RVDP pressure from 7 weeks preceding an event to peak of an event. Specifically, among the CHRONICLE patients, the daily median RVDP increased from an average of 17.1 mmHg at 2 weeks before the peak of a volume overload event to 19.2 mmHg on the day before the date of admission (defined as the peak). This represents a 12 % increase in RVDP over the 2 week period. In comparison, in these CHRONICLE group patients, average body weight was unchanged from 2 weeks prior to peak of the event, 241 lbs and 240 lbs respectively.

A similar pattern can be seen among the CONTROL group patients with average body weight increasing by about 1.1 lbs (0.5%) from 2 weeks before to the peak, while average RVDP increased by 1.4 mmHg or 7%. These findings are presented for the entire study cohort in Figure 6.

Figure 6. Comparison of IHM-measured RVDP and Patient-Reported Body Weights in the Time Leading Up to a Volume Overload Event



Consistent with previous reports of the reliability of using daily weights in the management of heart failure in the ambulatory setting, in the 3–7 day period preceding a HF-related event, sensitivity of weight appears to be poor.

Medication Interventions Related to Changes in Dynamic Intracardiac Pressures

Medication Changes

When information obtained from the IHM was routinely available, volume status changes could be more readily identified and addressed. On average, patients in the CHRONICLE arm experienced 35% more adjustments in their cardiovascular therapies than those in the CONTROL arm (p=0.0025). The majority of these adjustments were related to titration of diuretics, which were adjusted 53% more often using the IHM information in the CHRONICLE group.

Diuretic Adjustments

One hundred thirty patients were assessed as being optivolemic for a total of 491 months of follow-up, during which 558 diuretic adjustments were recorded, resulting in 1.14 adjustments per optivolemic patient-month. In contrast, patients classified in the hypervolemic state experienced 3.80 adjustments per hypervolemic patient-month. Likewise, patients classified in the hypovolemic state experienced 3.10 adjustments per hypovolemic patient-month.

Table 12. Diuretic Changes in the CHRONICLE Group by Volume State

	Hypovolemic States	Optivolemic States	Hypervolemic States
Cumulative Follow-Up (Months)	14	491	237
Number of Diuretic Adjustments	44	558	900
Diuretic Adjustments per Patient Month	3.10	1.14	3.80
		p=0.006	p<0.001

As expected, diuretic adjustments were appropriately and significantly increased or decreased when patients deviated from their own optivolemic state to either hyper- or hypovolemia. These results highlight the fact that diuretic adjustments were not arbitrarily increased in the CHRONICLE vs. the CONTROL group, but were rather systematically applied when appropriate as part of the overall management strategy evaluated in this study.

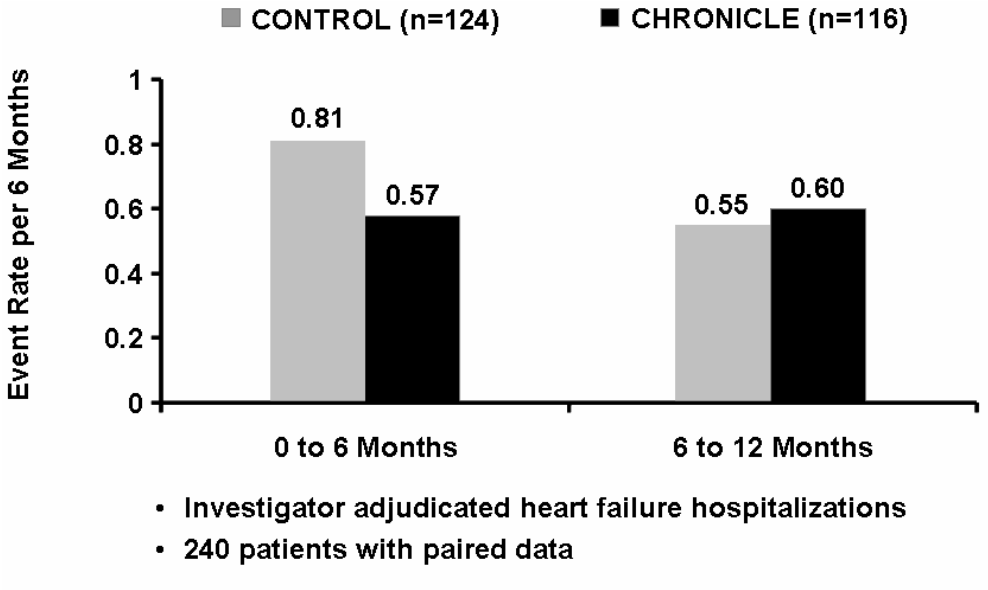
These results are consistent with the observation that 92% of all heart failure related events in the study were attributable to volume overload and with the premise of IHM Guided volume management. There was no

increase in adverse events in the CHRONICLE arm, and specifically no increase in those that might be attributed to excessive use of diuretics (e.g. dehydration or worsening renal function).

Long-term Effect of Chronicle Guided Care

As of January 31, 2006, paired data from 240 patients in the COMPASS-HF study was available for both the six months of randomized follow up as well as the subsequent six months where patients from both groups had IHM data available for their heart failure management. Heart failure event rates in the CHRONICLE group were consistent in both time periods, suggesting the continued successful implementation of IHM Guided Care beyond the requirements of the clinical protocol. Once IHM data became available for the management of CONTROL patients, their heart failure event rate declined from 0.81 during the six month randomized follow-up period to 0.55 during the subsequent six months, a rate similar to that observed in the CHRONICLE group.

Figure 7. Long-term Effect of CHRONICLE Guided Care



Post hoc Analyses

Several *post hoc* analyses were performed to provide additional insight into the impact of IHM Guided Care on heart failure management:

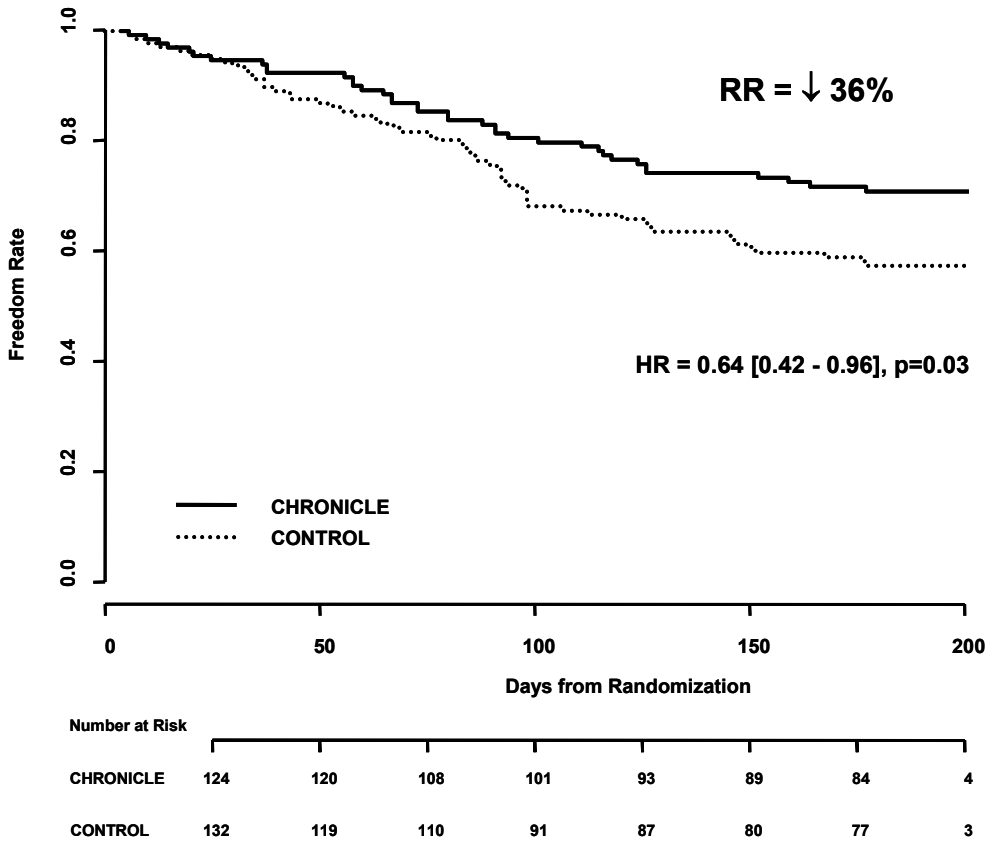
- A Cox proportional hazards analysis to estimate the reduction in the relative risk of a heart failure-related hospitalization, the predominant component of the primary effectiveness endpoint.
- A Cox proportional hazards analysis of the primary endpoint to estimate the reduction in the relative risk of a heart failure-related hospital equivalent.
- The COMPASS-HF study pre-specified that interaction between primary endpoint and various sub-groups would be examined. If an interaction was significant for any sub-group, the results of the primary endpoint would be reported for that sub-group. There were no *a priori* alpha adjustments pre-specified in the protocol.
- Multivariable analyses stemming from the observed differences between the NYHA III and IV patients with respect to outcome.

Relative Risk of a Heart Failure Hospitalization

The majority of heart failure events observed in the COMPASS-HF study were hospitalizations, and the relative risk of a heart failure-related hospitalization is a traditional endpoint used as a measure of morbidity in heart failure studies.

Out of the total 197 hospital equivalents that contributed to the analysis of the primary objective of COMPASS-HF, 171 (87%, as noted above) were hospitalizations for worsening heart failure. A Kaplan-Meier analysis was performed on this component of the primary endpoint. The results of the analysis showed a 36% reduction in the relative risk of a heart failure hospitalization in the CHRONICLE group compared to the CONTROL group, with a p-value of 0.03 (Figure 8).

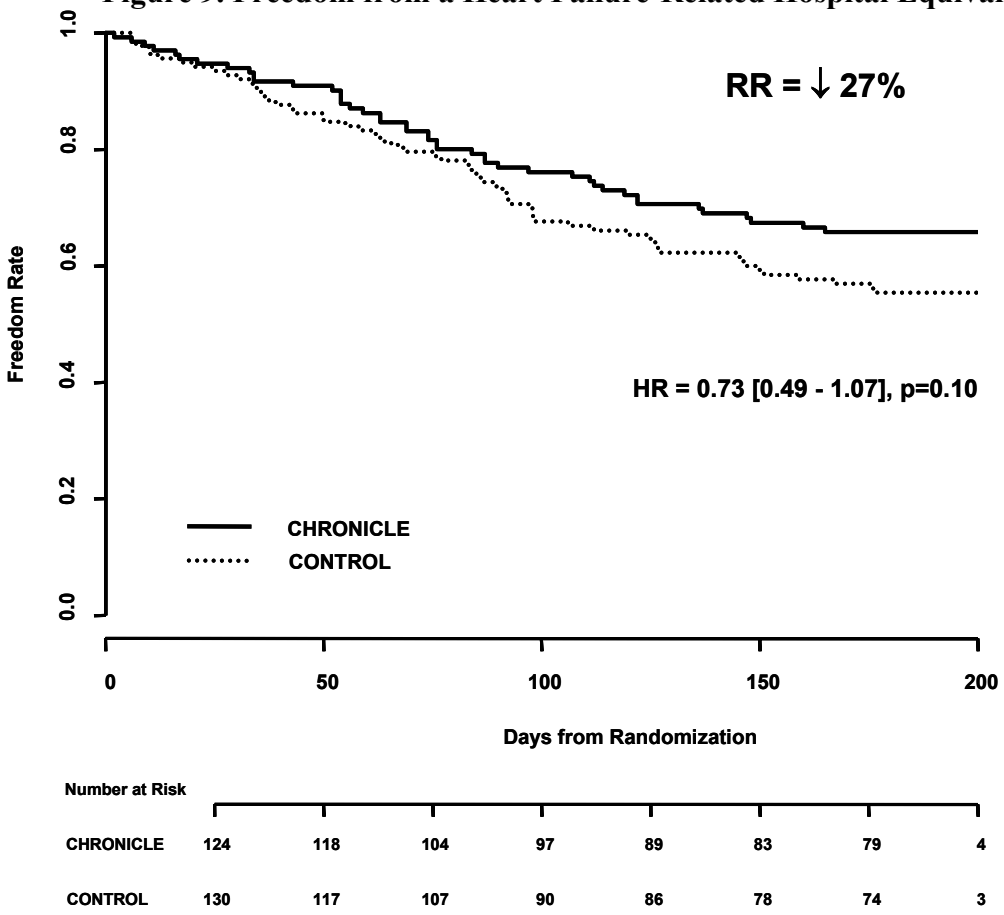
Figure 8. Freedom from a Heart Failure-Related Hospitalization



Relative Risk of a Heart Failure-Related Hospital Equivalent

Heart failure clinical studies traditionally employ a time-to-first event methodology in analyzing effectiveness endpoints, since it minimizes the impact that a few patients with a large number of events have on the overall average event rate. This analytical methodology was pre-specified in the COMPASS-HF statistical analysis plan, prior to the start of enrollment in the study. A Kaplan-Meier analysis of freedom from a heart failure-related hospital equivalent is presented below in Figure 9.

Figure 9. Freedom from a Heart Failure-Related Hospital Equivalent



There was a 27% reduction in the relative risk of a heart failure-related hospital equivalent, with a p-value of 0.10.

Interaction Between Key Pre-Specified Sub-groups and the Primary Endpoint

The protocol pre-specified the intent to assess the interaction between outcome and specific sub-groups, including patients with depressed left ventricular ejection fraction (LVEF < 50%) and patients with preserved left ventricular ejection fraction (LVEF ≥ 50%); etiology of heart failure (investigator determined); NYHA Class III and IV; history of coronary artery disease; and the presence of a cardiac rhythm management device. However, no hypotheses were pre-specified in relation to these sub-group analyses. Table 13 details the results of the primary objective within these subgroups.

Table 13. Results of Heart Failure-Related Hospital Equivalents (HE) Analysis by Sub-Group

	CHRONICLE			CONTROL			
Sub-group	HF Related HE	Months at Risk	Rate/6 months	HF Related HE	Months at Risk	Rate/6 months	P-value
LVEF< 50%	65	556	0.70	88	588	0.90	0.95
LVEF ≥ 50%	19	197	0.58	25	206	0.73	
Ischemic	46	347	0.79	60	351	1.03	0.86
Non-Ischemic	38	405	0.56	53	444	0.72	
NYHA Class III	58	644	0.54	99	700	0.85	0.08
NYHA Class IV	26	108	1.44	14	95	0.88	
History of CAD	52	412	0.76	73	429	1.02	0.65
No History of CAD	32	340	0.57	40	366	0.66	
No Concomitant Device	37	450	0.49	64	492	0.78	0.31
Concomitant Device	47	302	0.93	49	303	0.97	

Impact of IHM Guided Care in Patients With Preserved EF (LVEF≥50%)

Since volume overload is often a leading precipitating factor in heart failure hospitalizations in patients with depressed (defined as LVEF < 50%) or preserved ejection fraction (defined as an LVEF >=50%), it was expected that Chronicle IHM would accurately detect intracardiac pressures in both groups. The study therefore enrolled patients with both preserved and depressed ejection fractions. Seventy patients (26% of the study cohort) had a preserved ejection fraction at baseline evaluation.

To confirm the consistency of the impact of IHM Guided Care on the rate of heart failure events among patients with preserved or depressed left ventricular function, the COMPASS-HF study stratified randomization by baseline ejection fraction. Table 14 illustrates the results comparing the impact of IHM Guided Care in this sub-group of patients. Similar to the analysis of the primary endpoint in all study patients, event rates were estimated as the ratio of the total number of events to the total number of months at risk.

Table 14. Heart Failure-Related Events in Preserved vs. Depressed EF Patients

Adjudicated Heart Failure-Related Event Rate (per 6 Months)			
	Preserved EF (≥50%) (n=70)	Depressed EF (<50%) (N=204)	Total (n=274)
CONTROL Events	0.73	0.90	0.85
CHRONICLE Events	0.58	0.70	0.67
Relative Reduction	20%	22%	21%

These results demonstrate that CHRONICLE patients with either depressed or preserved ejection fraction experienced a similar magnitude of reduction in the rate of heart failure events compared to the CONTROL group during the six-month randomized follow-up period (20% for preserved EF patients versus 22% for depressed EF patients).

Impact of IHM Guided Care by Baseline NYHA Class

The effect of IHM Guided Care was consistent within all sub-groups, with the exception of NYHA classification. Despite the fact that the interaction between NYHA Class and outcome was not significant (p=0.08), the treatment effect in the NYHA class IV patients was directionally (qualitatively and quantitatively) different, whereby NYHA Class IV patients in the CHRONICLE group experienced a higher event rate compared to their CONTROL counterparts. The results of the primary effectiveness objective separated by NYHA Class is presented below.

Table 15. Summary of Primary Objective Results by NYHA Class

	NYHA Class III		NYHA Class IV	
	CHRONICLE	CONTROL	CHRONICLE	CONTROL
# of patients in study	112	122	22	18
# of patients with events	35	51	9	9
Total Hospital Equivalents	58	99	26	14
Hospitalizations	50	85	22	14
Emergency Dept. Visits	6	11	4	0
Urgent Heart Failure Clinic Visits	2	3	0	0
Event Rate per 6 Months	0.54	0.85	1.44	0.89
% Reduction in Event Rate	36% (p=0.06)		-63% (p=0.27)	

As this sub-group analysis illustrates, IHM Guided Care resulted in a 36% reduction in the rate of heart-failure events compared to the CONTROL among patients who were in NYHA Class III at baseline (p=0.06). In contrast, there is an increase in average rate of heart failure events among CHRONICLE patients in NYHA Class IV compared to CONTROL patients (p=0.27).

Multivariable Analyses

The following section includes a summary of multivariable analyses that were performed with the intent to determine whether the observed differences in outcome among NYHA Class III and IV patients was due to NYHA Class per se or other clinical factors predictive of outcome. The results of these analyses serve to provide additional insight into the influence of other potentially more objective baseline characteristics on outcome and are not intended to serve as a substitute for the pre-specified endpoints.

Specifically, the results of post-hoc analyses related to the following endpoints are presented:

- Difference in the rate of heart failure-related hospital equivalents (CHRONICLE vs. CONTROL)
- Relative risk of heart failure-related hospital equivalent (CHRONICLE vs. CONTROL)
- Relative risk of death or heart failure-related hospital equivalent (CHRONICLE vs. CONTROL)
- Relative risk of heart failure-related hospitalization (CHRONICLE vs. CONTROL)
- Relative risk of death or heart failure-related hospitalization (CHRONCILE vs. CONTROL).

Hypothesizing that some baseline characteristics are likely to be predictive of clinical outcome, the following steps were undertaken:

- Clinically important baseline characteristics including, but not limited to those that seemed to influence outcome among Class IV patients were identified. The intent in identifying these characteristics before any further analyses were conducted was to examine whether a strong association between these characteristics and outcome would emerge when considering all study patients (Class III and IV patients). The selected baseline characteristics are listed in **Table 16** below.
- To test the predictive relationship between the identified baseline characteristics and outcome, univariate analyses (negative binomial and Cox regressions) were conducted using all randomized study patients in the COMPASS-HF study. Characteristics with a p-value < 0.10 were then entered into a multivariable model (as shown in **Table 17**).
- Multivariable analyses provide an estimate of treatment effect after controlling for those characteristics that emerged as having a strong predictive relationship with outcome from the above described univariate step.

Results of the Univariate Analyses

The univariate statistics for all relevant baseline characteristics and the significance of their relationship with each of the following post-hoc outcomes are shown in Table 16 below. Bolded values indicate those covariates used in each multivariable analysis.

Table 16. Results of Univariate Regression Analyses

Baseline Characteristic	Univariate p-value				
	Rate of HF Hospital Equivalent	Relative Risk of HF Hospital Equivalent	Relative Risk of HF Hospitalization	Relative Risk of Death or HF Hospital Equivalent	Relative Risk of Death or HF Hospitalization
6-Minute Hall Walk	**<0.001**	**< 0.001**	**0.001**	**<0.001**	**<0.001**
ACE/ARB at Baseline	**0.04**	**0.001**	**0.002**	**0.002**	**<0.001**
Atrial Fibrillation	**<0.001**	**0.01**	**0.02**	**0.01**	**0.01**
Creatinine	**0.002**	**0.001**	**0.002**	**<0.001**	**<0.001**
LVEF	**0.07**	**0.09**	**0.06**	**0.06**	**0.02**
Number of Prior HF Events	**<0.001**	**0.001**	**0.04**	**<0.001**	**0.01**
QRS Duration	**0.07**	**0.04**	**0.06**	**0.01**	**0.01**
Quality of Life (MN Living with HF score)	**0.001**	**0.01**	**0.01**	**0.01**	**0.01**
Rales	**0.06**	**< 0.001**	**<0.001**	**0.001**	**<0.001**
Age	0.21	**0.07**	**0.05**	**0.02**	**0.01**
Concomitant Device	**0.05**	**0.07**	**0.07**	0.13	**0.08**
Etiology (Ischemic vs. Non-Ischemic)	0.11	**0.002**	**0.01**	**0.003**	**0.004**
Beta Blocker at Baseline	**0.07**	**0.07**	0.23	**0.04**	0.17
Hemoglobin	0.16	0.16	**0.05**	**0.06**	**0.02**
NYHA Class	**0.07**	0.21	0.23	**0.01**	**0.004**
Toprol XL Dose	**0.09**	0.12	**0.09**	0.11	**0.07**
Diabetes	**0.08**	**0.08**	0.15	0.26	0.32
Sodium	0.34	0.18	0.13	**0.06**	**0.03**
JVP	0.13	0.20	0.14	0.16	**0.10**

Baseline characteristics tested in the univariate analysis, but not significant at a level of $p<0.10$ for any of the analyses included: Carvedilol Dose, Diastolic/Systolic HF, Diuretic at Baseline, Enalapril Dose, Gender, JVP, Sodium, Spironolactone Dose, Systolic BP, and Years Diagnosed with HF.

As the univariate analyses demonstrate, there were several measures indicative of disease severity, including the number of heart failure-related events in the six months prior to baseline evaluation, six-minute hall walk, history of atrial fibrillation, self-reported heart failure-specific quality of life, serum creatinine, use of ACE inhibitor/ARB at baseline, and presence of a concomitant device.

Results of the Multivariable Analyses

Table 17 presents the results of the multivariable analyses for each of the post-hoc outcomes. For each analysis, the appropriate regression method used is listed. Each result is presented as a percent reduction in the CHRONICLE group compared to the CONTROL, with the hazard ratio (HR) and 95% confidence intervals (CI) noted as appropriate.

Table 17. Results of Multivariable Analyses

Analysis	Method	Covariates @ p<0.05		Covariates @ p<0.10	
		Reduction in CHRONICLE group (HR, CI)	P-Value	Reduction in CHRONICLE group (HR, CI)	P-Value
Rate of HF-Related Hospital Equivalents	Negative Binomial Regression	**28%** (-8% - 52%)	P = 0.11	**23%** (-16% - 48%)	P = 0.21
Freedom From HF-Related Hospital Equivalent	Cox Proportional Hazards Regression	**38%** (0.62, 0.41-0.94)	P = 0.02	**40%** (0.60, 0.40-0.92)	P = 0.02
Freedom From HF-Related Hospitalization	Cox Proportional Hazards Regression	**42%** (0.58, 0.38-0.89)	P = 0.01	**43%** (0.57, 0.37-0.89)	P = 0.01
Freedom From Death or HF-Related Hospital Equivalent	Cox Proportional Hazards Regression	**34%** (0.66, 0.45-0.97)	P = 0.03	**32%** (0.68, 0.46-1.01)	P = 0.06
Freedom From Death or HF-Related Hospitalization	Cox Proportional Hazards Regression	**35%** (0.65, 0.43-0.97)	P = 0.03	**33%** (0.67, 0.44-1.00)	P = 0.05

In summary, these post-hoc analyses suggest a consistent response to IHM-guided strategy in the COMPASS-HF study.

Adverse Events

Chronicle Phase I & II study Adverse Events

All adverse events were collected during the Chronicle Phase I & II study until approval of . Following the approval of this Amendment, adverse event collection for the Phase II Expansion patients was reduced to all serious, all cardiac-related and all system-related adverse events up to and including the 12 month follow-up visit. All Phase I and Phase II patients that had completed their 12 month follow-up visit were also included in the reduced adverse event collection.

With the approval of , adverse event collection was further reduced for all Phase I-II and Phase II Expansion patients post 12 month follow-up visit to include all serious and all system-related adverse events.

There were a total of 2,084 adverse events reported from over 6 years of follow-up in the 148 patients enrolled in the Chronicle Phase I & II study. Of these, 102 were classified as system or implant procedure related. The system/implant procedure related events were further classified as complications or observations per the following definitions from the Investigational Plan:

> **Observation**
> An observation is an adverse event which is resolved by non-invasive means such as medically or by reprogramming the device or which resolves spontaneously. All observations will be reported in the clinical report. Oral medications are considered "non invasive".
>
> **Complication**: A complication is an adverse event which is resolved invasively or which directly results in the death of or serious injury to the patient, the explant of the device or the termination of significant device function regardless of other treatments. Intravenous (IV) and intramuscular (IM) drug therapies are considered invasive treatment.

Table 18 details the reported adverse events that were classified as system or implant procedure related that were reported through December 31, 2004. All events were further classified as Complications or Observations; the event rates for each classification are reported as a percentage of the total device months of follow up. The percentage of patients affected is included as well.

Table 18. System or Implant Procedure Related Adverse Events Observed During Chronicle Phase I & II Study (148 Patients Implanted, 4257 Months of Follow Up)

Event	Number of Events	Patients Affected	% Complications per Month of Follow Up	% Observations per Month of Follow Up	% Patients with Events
lead failure	24	23	0.6 (24)	0 (0)	16%
excessive pain at pocket site	10	10	0 (0)	0.2 (10)	7%
inaccurate chronicle pressures	5	4	0.1 (5)	0 (0)	3%
lead dislodgement	5	4	0.1 (5)	0 (0)	3%
pocket hematoma	5	4	0 (1)	0.1 (4)	3%
pocket infection	3	3	0 (1)	0 (2)	2%
sensor failure; lead/system replacement	3	3	0.1 (3)	0 (0)	2%
artifact on pressure signal; lead repositioned	2	2	0 (2)	0 (0)	1%
AV re-entry tachycardia	1	1	0 (1)	0 (0)	1%
Chronicle not collecting data	1	1	0 (1)	0 (0)	1%
clot over pocket	1	1	0 (0)	0 (1)	1%
dehydration	1	1	0 (1)	0 (0)	1%
dyspnea / shortness of breath	1	1	0 (1)	0 (0)	1%
ecchymosis	1	1	0 (0)	0 (1)	1%
elevated Chronicle pressures	1	1	0 (1)	0 (0)	1%
endocardial trauma	1	1	0 (0)	0 (1)	1%
heart block requiring pacemaker during implant	1	1	0 (1)	0 (0)	1%
hematoma	1	1	0 (0)	0 (1)	1%

Table 18. System or Implant Procedure Related Adverse Events Observed During Chronicle Phase I & II Study (148 Patients Implanted, 4257 Months of Follow Up)

Event	Number of Events	Patients Affected	% Complications per Month of Follow Up	% Observations per Month of Follow Up	% Patients with Events
hypotension	1	1	0 (1)	0 (0)	1%
inadequate lead-IHM connection	1	1	0 (0)	0 (1)	1%
incision infection	1	1	0 (0)	0 (1)	1%
incisional pain	1	1	0 (0)	0 (1)	1%
lead artifact	2	2	0 (2)	0 (0)	1%
lead calibration problem at implant	1	1	0 (0)	0 (1)	1%
lead drift	2	2	0 (2)	0 (0)	1%
lead insulation break	1	1	0 (1)	0 (0)	1%
lead repositioning	1	1	0 (1)	0 (0)	1%
numbness/tingling	1	1	0 (1)	0 (0)	1%
pain (shoulder)	1	1	0 (0)	0 (1)	1%
pleuritic chest pain	1	1	0 (0)	0 (1)	1%
pneumothorax	2	2	0 (2)	0 (0)	1%
programmer software anomaly or failure	2	2	0 (0)	0 (2)	1%
prophylactic removal of device/lead for suspected infection	1	1	0 (1)	0 (0)	1%
sepsis	1	1	0 (1)	0 (0)	1%
site infection	1	1	0 (0)	0 (1)	1%
site pain	2	2	0 (0)	0 (2)	1%

Table 18. System or Implant Procedure Related Adverse Events Observed During Chronicle Phase I & II Study (148 Patients Implanted, 4257 Months of Follow Up)

Event	Number of Events	Patients Affected	% Complications per Month of Follow Up	% Observations per Month of Follow Up	% Patients with Events
site tenderness	2	2	0 (0)	0 (2)	1%
suspected lead conductor fracture	2	1	0 (2)	0 (0)	1%
sustained ventricular tachycardia	2	2	0 (1)	0 (1)	1%
swelling at pocket site	1	1	0 (0)	0 (1)	1%
temporary malfunction of system	1	1	0 (0)	0 (1)	1%
thrombus formation at lead	1	1	0 (1)	0 (0)	1%
ventricular fibrillation	1	1	0 (1)	0 (0)	1%
ventricular tachycardia	1	1	0 (0)	0 (1)	1%
wound dehiscence	1	1	0 (1)	0 (0)	1%

Table 19 below provides a detailed listing of the non-system, non-implant procedure related adverse events reported during the Phase I&II study through December 31, 2004. The table includes the number of patients affected, and the event rate observed per device months of follow up. Events reported in less than 2% of patients are not included in this table.

Table 19. Non-System, Non-Implant Related Adverse Events Observed During Chronicle Phase I & II and Phase II Expansion Study (148 Patients Implanted, 4257 Months of Follow Up)

Description of Event (Phase I&II)	Events Observed	Patients Affected	Events per month of follow up (%)	Patients affected (%)
worsening of congestive heart failure	308	111	7.2%	75.0%
dizziness	52	40	1.2%	27.0%
hypotension	52	38	1.2%	25.7%
dyspnea / shortness of breath	53	37	1.2%	25.0%
fatigue	44	36	1.0%	24.3%
syncope	50	36	1.2%	24.3%
non-specific chest pain	43	32	1.0%	21.6%
angina pectoris	67	29	1.6%	19.6%
hypokalemia	40	28	0.9%	18.9%
dehydration	31	25	0.7%	16.9%
anemia	41	21	1.0%	14.2%
hyperkalemia	30	21	0.7%	14.2%
renal failure	23	20	0.5%	13.5%
upper respiratory infection	20	19	0.5%	12.8%
depression	19	18	0.4%	12.2%
diarrhea	21	17	0.5%	11.5%
pneumonia	19	17	0.4%	11.5%
back pain	19	16	0.4%	10.8%
headache	21	16	0.5%	10.8%
renal insufficiency	24	16	0.6%	10.8%
insomnia	17	15	0.4%	10.1%
nausea	20	15	0.5%	10.1%
nausea/vomiting	17	15	0.4%	10.1%
non-sustained ventricular tachycardia	32	15	0.8%	10.1%
constipation	19	14	0.4%	9.5%
elevated laboratory values	16	14	0.4%	9.5%
palpitations	18	14	0.4%	9.5%
urinary tract infection	15	14	0.4%	9.5%

Description of Event (Phase I&II)	Events Observed	Patients Affected	Events per month of follow up (%)	Patients affected (%)
abdominal pain	14	12	0.3%	8.1%
bradycardia	15	12	0.4%	8.1%
cough	13	12	0.3%	8.1%
bronchitis	12	11	0.3%	7.4%
edema	12	11	0.3%	7.4%
fever	13	11	0.3%	7.4%
gout	11	11	0.3%	7.4%
volume overload	11	11	0.3%	7.4%
anxiety	10	10	0.2%	6.8%
diabetes	11	10	0.3%	6.8%
hyperglycemia	11	10	0.3%	6.8%
myocardial infarction	15	10	0.4%	6.8%
pain (shoulder)	10	10	0.2%	6.8%
hypoglycemia	14	9	0.3%	6.1%
paroxysmal atrial flutter / fibrillation	10	9	0.2%	6.1%
persistent atrial flutter / fibrillation	13	9	0.3%	6.1%
swelling	10	9	0.2%	6.1%
ventricular ectopy	14	9	0.3%	6.1%
weakness	10	9	0.2%	6.1%
anorexia	8	8	0.2%	5.4%
COPD exacerbation	14	8	0.3%	5.4%
epistaxis	9	8	0.2%	5.4%
head cold	8	8	0.2%	5.4%
hypertension	10	8	0.2%	5.4%
sustained ventricular tachycardia	9	8	0.2%	5.4%
atrial tachycardia	9	7	0.2%	4.7%
confusion	7	7	0.2%	4.7%
chest pain	7	6	0.2%	4.1%
fracture	7	6	0.2%	4.1%
indigestion	6	6	0.1%	4.1%
influenza	6	6	0.1%	4.1%
itching	6	6	0.1%	4.1%
pain (leg)	7	6	0.2%	4.1%
sudden cardiac death	6	6	0.1%	4.1%
ulcer	6	6	0.1%	4.1%
weight gain	7	6	0.2%	4.1%

Description of Event (Phase I&II)	Events Observed	Patients Affected	Events per month of follow up (%)	Patients affected (%)
cardiac arrest	6	5	0.1%	3.4%
ecchymosis	5	5	0.1%	3.4%
hyponatremia	5	5	0.1%	3.4%
infection	5	5	0.1%	3.4%
pain (arm)	5	5	0.1%	3.4%
agitation	4	4	0.1%	2.7%
body ache	6	4	0.1%	2.7%
cerebral vascular accident	5	4	0.1%	2.7%
earache	4	4	0.1%	2.7%
fall	4	4	0.1%	2.7%
gangrene	5	4	0.1%	2.7%
laceration	4	4	0.1%	2.7%
lightheadedness	4	4	0.1%	2.7%
near syncope	5	4	0.1%	2.7%
pleural effusion	4	4	0.1%	2.7%
pruritus	4	4	0.1%	2.7%
rash	4	4	0.1%	2.7%
sepsis	5	4	0.1%	2.7%
sinus infection	4	4	0.1%	2.7%
sinusitis	4	4	0.1%	2.7%
sleep apnea	4	4	0.1%	2.7%
spinal stenosis	4	4	0.1%	2.7%
abdominal cramping	3	3	0.1%	2.0%
abdominal distension	3	3	0.1%	2.0%
ankle injury	3	3	0.1%	2.0%
bleeding	3	3	0.1%	2.0%
blurred vision	3	3	0.1%	2.0%
cellulitis	4	3	0.1%	2.0%
chest pressure	3	3	0.1%	2.0%
emotional lability	3	3	0.1%	2.0%
gastritis	3	3	0.1%	2.0%
GERD	3	3	0.1%	2.0%
hematoma	3	3	0.1%	2.0%
leg cramping	3	3	0.1%	2.0%
mental status change	3	3	0.1%	2.0%
numbness	3	3	0.1%	2.0%

Description of Event (Phase I&II)	Events Observed	Patients Affected	Events per month of follow up (%)	Patients affected (%)
numbness/tingling	3	3	0.1%	2.0%
pacemaker implant	3	3	0.1%	2.0%
pain (groin)	5	3	0.1%	2.0%
pain (hip)	3	3	0.1%	2.0%
pain (neck)	4	3	0.1%	2.0%
pulmonary edema	3	3	0.1%	2.0%
site pain	5	3	0.1%	2.0%
tumor	3	3	0.1%	2.0%
viral illness	3	3	0.1%	2.0%
vomiting	3	3	0.1%	2.0%
weight loss	3	3	0.1%	2.0%

COMPASS-HF Adverse Events

As of January 31, 2006, there were a total of 77 deaths in the study. The cause of death and study period when the death occurred is indicated in the table below. No device-related deaths were observed.

Study Period	Number of Patient Deaths	Cause of Death		
		HF	CV (non-HF)	Other Cause
Screened/Enrolled but no implant procedure	2	0	2	0
After Unsuccessful Implant Procedure	0	0	0	0
After Implant, Not Randomized	0	0	0	0
During Randomization Period, CHRONICLE Group	13	6	4	3
During Randomization Period, CONTROL Group	11	3	7	1
After Randomization Period (All patients)	51	36	5	10
Total	**77**	**45**	**18**	**14**

Observed Adverse Events

All serious adverse events, all cardiovascular adverse events, and all adverse events related to the system (implantable hemodynamic monitor and pressure sensor) or the implant procedure were collected and are reported here through January 31, 2006. The Investigator reported adverse events by the primary event, its relatedness (cardiovascular, system, procedure, other), as well as its seriousness. Events were then further classified by the blinded Clinical Events Committee (CEC) for relatedness, seriousness, and by complications/observations for Chronicle System and Implant Procedure Related Events.

It is important to note that under this adjudication process, it is possible that an event reported by an Investigator on the case report form, could have been given a different, final adjudication (an Investigator-reported non-serious cardiovascular event that is adjudicated by the CEC as a serious non-system/non-procedure/non-cardiovascular event, for example). For this reason, similar event types listed under different classifications (e.g. hypotension events are found in procedure related events, as well as in cardiovascular events). The CEC adjudicated classifications were used to support the results of the study.

There were 530 adverse events reported during the randomization period. Of these, 431 were classified as complications or serious events, 99 were classified as

observations/non-serious events, and there were 24 deaths. The following table provides the incidence (in percent) of each type of event observed for the CHRONICLE and CONTROL groups during the randomized follow-up period.

Table 20 and Table 21 present the system and procedure related complications (respectively) observed during the course of the study through January 31, 2006. These data include events gathered on all 277 patients in whom an implant was attempted as part of the COMPASS-HF study. Results are stratified by those occurring during the 6-month randomized follow-up period and over the entire study period through January 31, 2006. Events observed during the randomized follow-period were further classified by CHRONICLE versus CONTROL.

Table 20. System Related Complications (COMPASS-HF)

System Related Complications – 37 events in 277 implant attempted patients						
	Events (pts)		**Event Rate per 6 months (months of follow – up)**		**Event Rate during Randomized Period (months of follow-up)**	
Event Type	**Implant to 6 Months**	**Post 6 Months**	**6 months (1620)**	**Overall (2789)**	**Chronicle (790)**	**Control (830)**
Lead dislodgement	15 (14)	4 (4)	0.06	0.03	0.05	0.06
Lead body damage	2 (2)	0 (0)	0.01	0.00	0.01	0.01
Artifact on waveform	4 (4)	1 (1)	0.01	0.01	0.01	0.02
Premature battery failure	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Pocket infection	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Pocket seroma	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Lead Migration	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Entrapped Lead	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Fibrosed Lead	0 (0)	2 (2)	0.00	0.00	0.00	0.00
Infection	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Deep Vein Thrombosis	0 (0)	2 (1)	0.00	0.00	0.00	0.00
Entrapped lead in the tricuspid valve	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Total	24 (23)	13 (12)				

Table 21. Procedure Related Complications

System/Procedure Related Complications – 16 events in 277 implant attempted patients						
	Events (pts)		Event Rate per 6 months (months of follow – up)		Event Rate during Randomized Period (months of follow-up)	
Event Type	**Implant to 6 Months**	**Post 6 Months**	**6 months (1620)**	**Overall (2789)**	**Chronicle (790)**	**Control (830)**
Pocket infection	2 (1)	1 (1)	0.01	0.00	0.00	0.01
Pocket hematoma	2 (2)	0 (0)	0.01	0.00	0.00	0.01
Paroxysmal atrial flutter/fibrillation	2 (2)	0 (0)	0.01	0.00	0.02	0.00
Pneumothorax	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Venous Occlusion	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Suture Abscess	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Non-specific chest pain	1 (1)	0 (0)	0.00	0.00	0.00	0.01
Cellulitis	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Clostridium Difficile	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Complete Heart Block	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Lead insertion	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Puncture of artery	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Total	15 (14)	1 (1)				

Table 22 presents the system and procedure related observations recorded during the course of the study through January 31, 2006. These data include events gathered on all 277 patients in whom an implant was attempted as part of the COMPASS-HF study. Results are stratified by those occurring during the 6-month randomized follow-up period and over the entire study period through January 31, 2006. Events observed during the randomized follow-period were further classified by CHRONICLE versus CONTROL.

Table 22. System and Procedure Related Observations

	Number Of Events (pts)		Event Rate per 6 months (months of follow–up)		Event Rate during Randomized Period (months of follow-up)	
Event Type	**Implant to 6 Months**	**Post 6 Months**	**6 months (1620)**	**Overall (2789)**	**Chronicle (790)**	**Control (830)**
System Related (8 events)						
Failure to sense	5 (4)	0 (0)	0.02	0.01	0.03	0.01
Lead body damage	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Pain at Incision Site	1 (1)	0 (0)	0.00	0.00	0.01	0.00
AV Node Disassociation	0 (0)	1 (1)	0.00	0.00	0.00	0.01
Procedure Related (21 events)						
Pocket hematoma	6 (6)	0 (0)	0.02	0.01	0.02	0.02
Pocket infection	4 (4)	0 (0)	0.01	0.01	0.02	0.01
Inability to Gain Venous Access	1(1)	0 (0)	0.00	0.00	0.00	0.00
Lead insertion	1 (1)	0 (0)	0.00	0.00	0.00	0.01
Extensive Bruising at Implant Site	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Transient Coronary Heart Block	1 (1)	0 (0)	0.00	0.00	0.00	0.01
Allergic Reaction	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Incisional Skin Tear	1 (1)	0 (0)	0.00	0.00	0.00	0.01
Sustained VT	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Hypotension	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Dizziness	1 (1)	0 (0)	0.00	0.00	0.00	0.01
Change in mental status	1 (1)	0 (0)	0.00	0.00	0.01	0.00
Deep Vein Thrombosis	1 (1)	0 (0)	0.00	0.00	0.00	0.01

Table 23 displays the cardiovascular related events (including HF related events) observed during the course of the COMPASS-HF study through January 31, 2006. Events and event rates are presented and stratified by CHRONICLE versus CONTROL patients.

Table 23. Cardiovascular Related (including HF related) Adverse Events in 274 randomized patients through January 31, 2006

	Randomized Data (0 – 6 Months) of events (pts)		Post Randomization (6+ months) of events (pts)		Randomized Data (0 – 6 Months) Rate per 6 months		Post Randomized Data (6+ months) Rate per 6 months	
Event Type	**CHRONICLE 134 patients**	**CONTROL 140 patients**	**CHRONICLE 117 patients**	**CONTROL 125 patients**	**CHRONICLE 790 months**	**CONTROL 830 months**	**CHRONICLE 1393 months**	**CONTROL 1396 months**
Serious Events (685 events)								
Decompensation of CHF	57 (35)	68 (43)	90 (50)	109 (45)	0.43	0.49	0.39	0.47
Volume overload	10 (6)	26 (16)	10 (8)	19 (12)	0.08	0.19	0.04	0.08
Volume depletion/dehydration	6 (6)	6 (5)	6 (5)	5 (5)	0.05	0.04	0.03	0.02
Cardiovascular procedure	4 (4)	6 (5)	13 (13)	13 (12)	0.03	0.04	0.06	0.06
Hypotension	1 (1)	4 (4)	3 (3)	3 (3)	0.01	0.03	0.01	0.01
Non-specific chest pain	4 (3)	4 (4)	11 (9)	6 (5)	0.03	0.03	0.05	0.03
Non sustained VT	1 (1)	3 (3)	3 (3)	3 (3)	0.01	0.02	0.01	0.01
Sustained VT	1 (1)	3 (3)	3 (3)	7 (5)	0.01	0.02	0.01	0.03
Acute MI/Cardiac arrest	3 (3)	3 (3)	6 (6)	5 (4)	0.02	0.02	0.03	0.02
Atrial tachycardia	0 (0)	1 (1)	1 (1)	1 (1)	0.00	0.01	0.00	0.00
Paroxysmal atrial flutter/fibrillation	4 (3)	2 (2)	4 (4)	4 (3)	0.03	0.01	0.02	0.02
Persistant atrial flutter/fibrillation	1 (1)	1 (1)	2 (2)	3 (2)	0.01	0.01	0.01	0.01
Ventricular fibrillation/flutter	2 (2)	2 (2)	1 (1)	2 (2)	0.02	0.01	0.00	0.01
Hypertension	1 (1)	2 (2)	0 (0)	0 (0)	0.01	0.01	0.00	0.00
Angina pectoris	8 (8)	1 (1)	12 (7)	4 (4)	0.06	0.01	0.05	0.02
Renal insufficiencies/failure	2 (2)	1 (1)	1 (1)	0 (0)	0.02	0.01	0.00	0.00
Pneumonia	1 (1)	1 (1)	2 (2)	3 (2)	0.01	0.01	0.01	0.01

Table 23. Cardiovascular Related (including HF related) Adverse Events in 274 randomized patients through January 31, 2006

	Randomized Data (0 – 6 Months) of events (pts)		Post Randomization (6+ months) of events (pts)		Randomized Data (0 – 6 Months) Rate per 6 months		Post Randomized Data (6+ months) Rate per 6 months	
Event Type	**CHRONICLE 134 patients**	**CONTROL 140 patients**	**CHRONICLE 117 patients**	**CONTROL 125 patients**	**CHRONICLE 790 months**	**CONTROL 830 months**	**CHRONICLE 1393 months**	**CONTROL 1396 months**
Ascites	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Stroke	1 (1)	1 (1)	1 (1)	0 (0)	0.01	0.01	0.00	0.00
Electro Mechanical Dis-association	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Hyponatremia	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Hypokalemia	0 (0)	2 (2)	0 (0)	1 (1)	0.00	0.01	0.00	0.00
Elective Surgery	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Inhalant Poisoning from Cleaning Agents	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Sudden Cardiac Death	1 (1)	1 (1)	1 (1)	0 (0)	0.01	0.01	0.00	0.00
Death, unknown cause	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Shaking and Chills	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Multi-system Organ Failure	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
AV nodal tachycardia	0 (0)	0 (0)	2 (2)	0 (0)	0.00	0.00	0.01	0.00
Syncope/near syncope	0 (0)	0 (0)	5 (5)	1 (1)	0.00	0.00	0.02	0.00
Dyspnea/SOB	2 (2)	0 (0)	1 (1)	0 (0)	0.02	0.00	0.00	0.00
Dizziness	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Bradycardia	0 (0)	0 (0)	0 (0)	2 (2)	0.00	0.00	0.00	0.01
Edema/weight gain	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Lab value abnormalities	3 (3)	0 (0)	4 (4)	1 (1)	0.02	0.00	0.02	0.00
Worsening COPD	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Pulmonary hypertension	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Pulmonary embolism	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Pulmonary edema	1 (1)	0 (0)	0 (0)	2 (2)	0.01	0.00	0.00	0.01
Anemia	1 (1)	0 (0)	0 (0)	1 (1)	0.01	0.00	0.00	0.00
Diabetes	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00

Table 23. Cardiovascular Related (including HF related) Adverse Events in 274 randomized patients through January 31, 2006

	Randomized Data (0 – 6 Months) of events (pts)		Post Randomization (6+ months) of events (pts)		Randomized Data (0 – 6 Months) Rate per 6 months		Post Randomized Data (6+ months) Rate per 6 months	
Event Type	**CHRONICLE 134 patients**	**CONTROL 140 patients**	**CHRONICLE 117 patients**	**CONTROL 125 patients**	**CHRONICLE 790 months**	**CONTROL 830 months**	**CHRONICLE 1393 months**	**CONTROL 1396 months**
Transient ischemic attack	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Nausea/vomiting	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Urinary Tract Infection	1 (1)	0 (0)	1 (1)	1 (1)	0.01	0.00	0.00	0.00
Diaphragmatic pacing	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Pleural effusion	1 (1)	0 (0)	0 (0)	1 (1)	0.01	0.00	0.00	0.00
Change in mental status	2 (1)	0 (0)	0 (0)	0 (0)	0.02	0.00	0.00	0.00
Infection	0 (0)	0 (0)	1 (1)	2 (1)	0.00	0.00	0.00	0.01
Hyperkalemia	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Respiratory Failure/Arrest	1 (1)	0 (0)	1 (1)	1 (1)	0.01	0.00	0.00	0.00
MRSA Infection	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Sepsis	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Cardiac Transplant	1 (1)	0 (0)	3 (3)	2 (2)	0.01	0.00	0.01	0.01
Elective Diagnostic Procedure	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Peripheral Vascular Disease	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Allergic Reaction	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Complete Heart Block	0 (0)	0 (0)	1 (1)	1 (1)	0.00	0.00	0.00	0.00
Deep Vein Thrombosis	0 (0)	0 (0)	0 (0)	2 (2)	0.00	0.00	0.00	0.01
Hypoglycemia	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Pericardidis	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Hospitalization for Transplant, then Cancelled	0 (0)	0 (0)	0 (0)	2 (1)	0.00	0.00	0.00	0.01
Coronary Artery Disease	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Hemothorax	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00

Table 23. Cardiovascular Related (including HF related) Adverse Events in 274 randomized patients through January 31, 2006

	Randomized Data (0 – 6 Months) of events (pts)		Post Randomization (6+ months) of events (pts)		Randomized Data (0 – 6 Months) Rate per 6 months		Post Randomized Data (6+ months) Rate per 6 months	
Event Type	**CHRONICLE 134 patients**	**CONTROL 140 patients**	**CHRONICLE 117 patients**	**CONTROL 125 patients**	**CHRONICLE 790 months**	**CONTROL 830 months**	**CHRONICLE 1393 months**	**CONTROL 1396 months**
Accidental Drug Overdose	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Drug Pump Malfunction	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Unwitnessed Death	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Non Serious Events (111 events)								
Paroxysmal atrial flutter/fibrillation	1 (1)	1 (1)	0 (0)	1 (1)	0.01	0.01	0.00	0.00
Persistant atrial flutter/fibrillation	0 (0)	0 (0)	2 (2)	1 (1)	0.00	0.00	0.01	0.00
AV nodal tachycardia	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Ventricular ectopy	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Non sustained VT	1 (1)	1 (1)	1 (1)	2 (2)	0.01	0.01	0.00	0.01
Sustained VT	0 (0)	2 (2)	0 (0)	1 (1)	0.00	0.01	0.00	0.00
Ventricular fibrillation/flutter	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Hypotension	2 (2)	0 (0)	0 (0)	0 (0)	0.02	0.00	0.00	0.00
Decompensation of CHF	6 (5)	5 (5)	2 (2)	8 (7)	0.05	0.04	0.01	0.03
Syncope/near syncope	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Angina pectoris	3 (2)	1 (1)	2 (2)	2 (2)	0.02	0.01	0.01	0.01
Non-specific chest pain	1 (1)	3 (2)	0 (0)	6 (3)	0.01	0.02	0.00	0.03
Dyspnea/SOB	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Palpitations	1 (1)	1 (1)	0 (0)	0 (0)	0.01	0.01	0.00	0.00
Fatigue/tiredness	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Dizziness	1 (1)	1 (1)	0 (0)	0 (0)	0.01	0.01	0.00	0.00
Bradycardia	1 (1)	1 (1)	0 (0)	2 (2)	0.01	0.01	0.00	0.01
Edema/weight gain	0 (0)	2 (2)	0 (0)	0 (0)	0.00	0.01	0.00	0.00

Table 23. Cardiovascular Related (including HF related) Adverse Events in 274 randomized patients through January 31, 2006

	Randomized Data (0 – 6 Months) of events (pts)		Post Randomization (6+ months) of events (pts)		Randomized Data (0 – 6 Months) Rate per 6 months		Post Randomized Data (6+ months) Rate per 6 months	
Event Type	**CHRONICLE 134 patients**	**CONTROL 140 patients**	**CHRONICLE 117 patients**	**CONTROL 125 patients**	**CHRONICLE 790 months**	**CONTROL 830 months**	**CHRONICLE 1393 months**	**CONTROL 1396 months**
Volume depletion/dehydration	2 (2)	3 (3)	1 (1)	0 (0)	0.02	0.02	0.00	0.00
Volume overload	4 (4)	10 (6)	1 (1)	2 (2)	0.03	0.07	0.00	0.01
Renal insufficiencies/failure	1 (1)	1 (1)	0 (0)	0 (0)	0.01	0.01	0.00	0.00
Transient ischemic attack	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Cardiovascular procedure	0 (0)	0 (0)	1 (1)	2 (2)	0.00	0.00	0.00	0.01
Diaphragmatic pacing	0 (0)	1 (1)	0 (0)	0 (0)	0.00	0.01	0.00	0.00
Chest tightness	1 (1)	0 (0)	0 (0)	0 (0)	0.01	0.00	0.00	0.00
Elective Surgery	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
CV Drug Related Side Effect	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Hyperlipidemia	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Splenic Infarct	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Deep Vein Thrombosis	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Abdominal Aortic Aneurysm	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Urinary Retention	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00
Tachy Arrhythmia	0 (0)	0 (0)	1 (1)	0 (0)	0.00	0.00	0.00	0.00
Wound Bleeding	0 (0)	0 (0)	0 (0)	1 (1)	0.00	0.00	0.00	0.00

Potential Risks

Potential risks include (but are not limited to): the inability of the device to operate due to the lead breaking or dislodging within the heart; the possibility of the lead damaging cardiac tissue; lead conductor or insulation fracture; valve damage; valve entanglement; thrombolytic and air embolism; air entering a vein during insertion of the lead leading to pulmonary embolism; venous or cardiac perforation; cardiac tamponade; pericardial effusion; extracardiac muscle or nerve stimulation; heart or vein wall rupture; cardiac dissection; pericardial rub; monitor malfunction; erosion of the pocket; infection; myocardial irritability; endocarditis; thrombosis; transvenous lead-related thrombosis; hematoma/seroma; embolism; pneumothorax; the induction of an arrhythmia; heart block; tissue overgrowth of the lead or signal artifact causing the system to become ineffective; intermittent or continuous loss of sensing; localized pain after surgery; rejection phenomena (local tissue reaction, fibrotic tissue formation, device migration); or death.

For a patient with a pre-existing pacemaker or ICD, risks may include complications arising from additional lead placement such as dislodgement of the existing leads.

The risks described above are minimized by assuring the implants and procedures are performed by experienced physicians and supported by experienced medical staff.

Conclusions Drawn from Clinical and Non-Clinical Studies

1. This clinical report represents the cumulative experience with the Chronicle IHM system in 422 patients, with an aggregate follow-up of over 700 patient-years commencing with the first implant of the Chronicle Phase I study in 1998.

2. Early studies confirmed the feasibility of placing a chronic pressure sensor in the right ventricle, continuously recording intracardiac pressures, and storing these data in an implantable hemodynamic monitor.

3. Rigorous, invasive and provocative testing performed during the Chronicle Phase I & II study confirmed the accuracy, validity and reliability of the Chronicle IHM system. All pre-specified performance objectives in the Phase I & II study were met.

4. The Chronicle Phase I & II study identified a consistent pattern of rising intracardiac pressures in the days and weeks leading up to worsening heart failure events, suggesting that frequent review of these data may be useful in preventing acute exacerbations.

5. Following a retrospective review of the pressure data collected during the early stages of the Phase I & II study, investigators crafted and tested the IHM-guided patient management strategy. This framework allowed clinicians to optimize medication and fluid balance by using intracardiac pressures to assess volume status and intervene accordingly through the implementation of existing guidelines and evidence-based therapies.

6. Having established the accuracy, reliability and clinical relevance of intra-cardiac pressures, a study was designed to further elucidate the impact of IHM Guided Care in a randomized controlled study called COMPASS-HF.

7. The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study was a multi-center, randomized, single-blind, parallel controlled trial that was designed to assess the clinical impact of an IHM-based management strategy in patients with advanced heart failure who were already receiving standard medical care. The study incorporated several unique aspects that charted new ground in heart failure management and clinical trial design:
   - The study implemented and tested a novel heart failure management strategy using objective IHM-derived information that describes the patient's dynamic volume state while outside of a medical facility and performing activities of daily living.
   - The Chronicle IHM is not a heart failure therapeutic modality; rather, it provides information that allows clinicians to appropriately adjust proven interventions and better regulate volume. Thus, COMPASS-HF was designed to test the clinical utility of an IHM-guided patient management strategy that is based on hemodynamic data to optimize medications, diet and fluid balance. As a strategy complementary to existing heart failure care, IHM Guided Care was integrated into the heart failure management practice of each participating center.

- COMPASS-HF utilized a new outcome measure that was intended to include not only the recognized endpoint of hospitalization but also urgent visits that might be increased due to physician concern about abnormal hemodynamics reported from the Chronicle IHM.
- All patients in COMPASS-HF received a Chronicle IHM, but none of the CONTROL patients were managed using information from the IHM until their six-month randomized follow-up visit was completed. In order to keep the patients blinded to their management strategy (i.e. with or without Chronicle IHM), CONTROL patients were frequently contacted to match the intensive communication schedule observed in the CHRONICLE group. This strategy was highly effective as indicated by a survey implemented at the end of the 6-month, blinded randomized period showing that 63% of the CONTROL patients thought that they were being managed by information from the IHM (75% of the CHRONICLE patients indicated that they believed they were being managed using IHM Guided Care). This result underscores the successful efforts to maintain blinding in executing a challenging study design.
- COMPASS-HF enrolled patients with either depressed (<50%) or preserved (≥50%) ejection fraction, since: (1) volume overload is often a precipitating factor for heart failure hospitalizations in either group, and (2) it was expected that the Chronicle IHM would be able to accurately determine intracardiac pressures in both groups.

8. COMPASS-HF pre-specified primary safety objectives:
   - The freedom from system-related complications through six months was 91.5% with a lower one-sided 95% confidence bound of 88.7% - meeting the pre-specified performance criterion of 80%.
   - The freedom from pressure sensor failure through six months was 100% with a lower one-sided 95% confidence bound of 98.9% - meeting the pre-specified performance criterion of 90%.

9. COMPASS-HF pre-specified primary effectiveness objective:
   - It was hypothesized that the CHRONICLE group would experience a significantly lower rate of heart failure-related events (hospitalizations, emergency department visits, and urgent clinic visits requiring intravenous therapy for heart failure) compared to the CONTROL group.
   - Overall, 44 patients experienced 84 heart failure-related events in the CHRONICLE group, and 60 patients experienced 113 heart failure-related events in the CONTROL group during the randomized follow-up period, resulting in event rates of 0.67 and 0.85 in the CHRONICLE and CONTROL groups, respectively. This 21% reduction in the rate of heart failure-related events did not reach statistical significance (p=0.33), as analyzed by the negative binomial regression methodology.

- There were two key assumptions in estimating the sample size requirements in COMPASS-HF that may have affected the ability of the trial to meet the primary effectiveness endpoint. These assumptions include:

  1) Average CONTROL event rate of 1.2:
  The observed average event rate in COMPASS-HF was 0.85, significantly lower than the hypothesized rate of 1.2, reflecting in part the diligent efforts to maintain blinding in the CONTROL group by an equivalently intensive rate of patient contact as in the CHRONICLE group.

  The premise of IHM Guided Care is that when clinicians are able to continuously monitor hemodynamic data, they are afforded the opportunity to intervene sooner and potentially abort an evolving episode of decompensated heart failure. Because they would have more real-time information, it was anticipated that clinicians would communicate more frequently with patients randomized to the CHRONICLE group than they would with patients in the CONTROL group. To ensure balanced communication between clinicians and patients in both groups, random and scheduled surveillance calls to patients in the CONTROL group were incorporated into the study procedures. Each patient in both study groups was contacted, on average, 25 times during the six-month randomized follow-up period. Since frequent patient contact with heart failure management teams has previously been shown to reduce hospitalizations27-28, it is likely that this increased level of interaction, which is not usually seen in most heart failure programs, contributed to the relatively low average event rate observed in the CONTROL arm (0.85 vs. the hypothesized 1.2 events per six months, and vs. 1.9 in the six months prior to enrollment in COMPASS-HF).

  2) Events would follow a Poisson distribution:
  The sample size of the COMPASS-HF study was determined under the assumption that the incidence of heart failure events in the CONTROL group would follow a Poisson distribution29, with an average rate of 1.2 events per patient over a six-month period and a variance of 1.2. While the average rate of heart failure events observed in the CONTROL group was 0.85, the observed variance was 2.3. The fact that the observed variance was nearly three times greater than the mean suggested the need to apply an alternative pre-specified analytical methodology more consistent with the observed distribution of heart failure events in the study (i.e. negative binomial instead of Poisson regression).

  The combined effect of the rigorous blinding policy that likely resulted in a lower than anticipated CONTROL event rate, and the greater than anticipated variability in the incidence of heart failure events resulted in an overall loss of power (68% actual versus 80% hypothesized) that likely hindered the ability of the trial to meet its primary endpoint.

10. Post-hoc analyses of effectiveness:
    - Analysis of the relative risk of a heart failure-related hospitalization revealed a 36% reduction (p=0.03) in favor of IHM Guided Care.
    - Long-term results demonstrated a consistent reduction in average event rate among CONTROL patients once IHM Guided Care was implemented, with CHRONICLE patients maintaining the reduction observed during the randomized follow-up period.

11. Summary of Physiologic Basis for Hemodynamic Monitoring to Improve Heart Failure Management:
    - Moderate to advanced heart failure patients in the COMPASS-HF study sustained a consistent increase in intracardiac pressures in the days and weeks preceding admission for symptomatic decompensation.
    - Filling pressures are not reliably reflected by weights. Daily weights were neither correlated with intracardiac pressures nor was there a consistent increase in the days leading to decompensated heart failure. These results suggest that intracardiac pressures may be a more sensitive tool in the detection of pending decompensations, although rapid weight gain in the days leading to an event may be highly specific.
    - An IHM-guided management strategy resulted in significantly more adjustments in diuretics among patients in the CHRONICLE group compared to patients in the CONTROL group.
    - There was no increase in adverse events in the CHRONICLE group that might be attributed to the excessive use of diuretics (e.g. dehydration or worsening renal function).
    - These results substantiate the dynamic nature of intracardiac pressures, their relationship to decompensated heart failure, and the utility of continuous intracardiac pressure monitoring in the ambulatory management of moderate to advanced heart failure, where hypervolemia is the predominant reason for heart failure morbidity.

12. For the first time, the Chronicle IHM system enables continuous ambulatory monitoring of a patient's hemodynamic status, instead of the current approach of a management strategy based on "snapshot" assessments, limited largely to the clinic or inpatient setting.

13. When considering the demonstrated accuracy, reliability and safety of the IHM system, the direction of the primary effectiveness endpoint, and the relationship between changes in hemodynamics and worsening heart failure, on balance, an IHM-guided management strategy can serve as a useful addition to the current management of patients with moderate to advanced heart failure.