# FDA Executive Summary Memorandum

Prepared for the March 1, 2007, meeting of the
Circulatory System Devices Advisory Panel

P050032
Medtronic, Inc.
Chronicle Implantable Hemodynamic Monitor (IHM) System

## 1. PROPOSED INDICATIONS FOR USE

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 in these patients.

## 2. DEVICE DESCRIPTION

The Chronicle Implantable Hemodynamic Monitor (IHM) combined with the Chronicle Pressure Sensing Lead measures and stores hemodynamic data, heart rate, activity, and temperature for the ambulatory patient. The patient also carries an external pressure reference, Chronicle Tracker, which corrects the intracardiac pressure data for any changes in the barometric pressure.

The Chronicle IHM and Chronicle Tracker data can be obtained through the programmer (for in-office visits) or viewed on the web-based Medtronic CareLink Network. The patient uses the Medtronic CareLink Monitor for Chronicle Systems to send Chronicle IHM and Chronicle Tracker data via a phone line in their home to the Medtronic CareLink Network. The data are then stored on the secure Medtronic CareLink Network for clinician viewing. Use of the data will allow clinicians to assess a patient's hemodynamic status, and make clinical decisions to better manage a patient's heart failure.

Please refer to the System Description section of this panel pack (provided by Medtronic) for further details.

## 3. REGULATORY HISTORY

Medtronic's clinical investigations for the Chronicle Implantable Hemodynamic Monitor (IHM) System began in May 1995 under IDE G950062 (approved May 12, 1995) as a feasibility study. This study incorporated a multi-center, prospective, non-randomized study design. Phase I was self-controlled utilizing paired data of the IHM and pressure measurements taken simultaneously using a Swan-Ganz catheter and was intended to assess the effectiveness of the IHM at making accurate intracardiac pressure measurements. Phase I enrolled 32 patients at 4 centers; 2 in the United States and 2 outside the United States.

Phase II required a reduced follow-up and procedure schedule, namely the elimination of Swan-Ganz catheterizations. Patients were seen in the clinic every other month. The primary intention of this phase was to assess safety of the implanted system and to gain experience with the clinical utility of the Chronicle IHM. All study patients enrolled in Phase I, II and II Expansion are being followed every six months. Overall, 116 patients were enrolled during the Chronicle Phase II and Expansion study, totaling 148 (116 + 132) patients in the Chronicle Phase I & II study. Please refer to the Clinical Experience section of this panel pack, prepared by the sponsor, for a detailed discussion of the Phase I & II studies.

Clinical evaluation of the COMPASS-HF study began with the first implant occurring on March 18, 2003. The purpose of this randomized study was to evaluate the safety and effectiveness of Chronicle Guided Care (CGC) in patients with moderate to severe heart failure. This study incorporated a prospective, multi-center, randomized, single-blind, parallel controlled design.

A pre-filing and expedited review request meeting was held with FDA on April 4, 2005. At the meeting, FDA reiterated the position that was conveyed early in the IDE review process regarding a minimum number of patients with 6 months of follow-up. Accordingly, FDA advised the sponsor that the PMA could not be filed until 226 patients were followed for 6 months in the COMPASS-HF Trial. The COMPASS-HF clinical report included in this PMA reports on all 274 randomized patients, with all patients that have not died or exited the study having completed a 6-month follow-up visit (245 patients).

## 4. PRE-CLINICAL STUDIES

### a. Pressure Sensing Leads

The sponsor conducted a series of pre-clinical tests using the Model 4328A Pressure Sensing Leads.

- Thermal Shock
- Tip Protector Removal
- Stylet Insertion/Withdrawal
- Stylet Bottoming/Mismatch
- Stylet Perforation
- Fluid Leakage
- Introducer Compatibility
- Tip Stiffness
- Visual Inspection
- Composite Tensile Integrity
- Dry IS-1 Connector Insertion/Withdrawal
- Wet IS-1 Connector Insertion/Withdrawal
- Composite Tensile Strength
- Anchoring Sleeve Suturing Test
- Lead Body Flex
- Connector Flex Testing
- Composite Distal Fatigue
- DC Resistance
- IS-1 Connector Leakage
- Electrical Functional Testing
- Electrochemical Impedance Spectroscopy (EIS)
- Intermittency
- Pressure Cycle Testing
- Packaging Testing

Pre-clinical testing for the Model 4328B lead was limited to those tests that could have been affected by the differences between the Model 4328A and 4328B leads. While the results of most of the above tests are applicable to the revised leads, the following tests were repeated using the 4328B leads.

- Thermal Shock
- Fluid Leakage Test
- Visual Inspection
- IS-1 Connector Leakage
- Electrical Functional Test
- Intermittency
- Packaging Testing

FDA has completed its review of the preclinical test reports submitted for the pressure sensing leads; there are no remaining concerns.

**b. Software**

FDA has conducted a comprehensive review of the verification and validation testing conducted in support of the software involved in the following system components:

- Model 9520B Chronicle Implantable Hemodynamic Monitor (IHM)
- Model 9982 v 2.0 Application Software for the Chronicle Model 9520B
- Model 2090 Physician Programmer
- Model 2955HF Chronicle Tracker External Pressure Reference (EPR)
- Model 2490F Medtronic CareLink Monitor for Chronicle Systems
- Medtronic CareLink Network
- Model 2491 Device Data Management Application

The sponsor provided a complete and thorough description of the operation and validation of the firmware and software of the Chronicle IHM System. FDA has no remaining concerns.

**c. Pre-Clinical Testing of Other Components**

The sponsor provided pre-clinical testing reports to characterize the following aspects of the Model 9520B Chronicle IHM device performance:

- Pressure Accuracy
- Interference with Concomitant Implants
- Environmental Qualification Assessment
- Battery Testing
- Current Drain
- Connector Qualification
- Feedthrough Test
- Shelf Life
- Packaging

The sponsor provided pre-clinical testing reports to characterize the following aspects of the Model 2955HF Chronicle Tracker External Pressure Reference device performance:

- Electromagnetic Compatibility Emissions
- Electromagnetic Immunity
- Pressure Sensor Drift
- Battery Longevity
- Packaging

FDA has reviewed these test reports and has no remaining concerns.

**d. Sterilization**

The Chronicle IHM System contains only two sterile components: the Model 9520B Chronicle Implantable Hemodynamic Monitor and the Model 4328A & 4328B Chronicle Pressure Sensing Leads (PSL). After reviewing the information submitted by the sponsor, FDA has concluded that Medtronic has satisfactorily documented the adoption of the Chronicle IHM and PSL into the existing validated Ethylene Oxide (EO) sterilization processes at their manufacturing facilities. The currently approved and validated EO sterilization cycles should render product to a sterility assurance level (SAL) of $10^{-6}$ for the Chronicle IHM and PSL when the cycle conditions are followed.

FDA has no remaining concerns.

**e. Biocompatibility**

The sponsor has certified that all tissue or fluid contacting materials used in the Model 9520B Chronicle IHM and Pressure Sensing Leads are identical to materials used in devices previously reviewed and approved by FDA. Because this in an original PMA, the sponsor was also asked to provide the following information:

a. Table identifying all the generic materials by chemical name, supplier trade name, supplier name, and device component location;

b. Sufficient processing information to include any materials (and amounts) that could have an impact on biocompatibility; and

c. For the pressure sensing lead, a list of the biocompatibility tests that were performed on the devices cited in the sponsor's certification.

This information has been reviewed by FDA and there are no remaining concerns.

**f. Manufacturing**

FDA has reviewed this information and has no remaining concerns.

## 5. PIVOTAL CLINICAL STUDY

The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study incorporated a prospective, multi-center, randomized, single-blind, parallel controlled design. The COMPASS-HF study enrolled 274 patients at 28 participating sites in the United States.

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 best available heart failure medical and device therapy augmented by the use of Chronicle data, specifically trended right ventricular (RV) systolic and diastolic pressure and estimated pulmonary artery diastolic pressure (ePAD), heart rate and activity data. Patients randomized to the CONTROL group were treated with best 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 6 months, stored on the Chronicle Information Network, and patients were seen in the clinic for a protocol-required visit every six months thereafter. Patients will continue to be followed in the clinic every six months.

### a. Inclusion Criteria

- Patient provides written informed consent
- Patient is 18 years of age or older
- Patient has been classified as New York Heart Association (NYHA) Class III or Class IV at baseline evaluation
- Patient has been 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
- Patient must have 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 6 months prior to baseline evaluation
- Patient is willing and able to comply with the protocol, including sending weekly remote monitor transmissions, completing required testing (with the exception of the 6 minute hall walk test if the patient is unable to ambulate for reasons other than heart failure) and attend follow-up visits

### b. Exclusion Criteria

- Patients who are, in the opinion of the investigator, likely to be transplanted within 6 months from randomization or will remain hospitalized until transplantation

- Patients with severe COPD or severe restrictive airway disease (recommend FEV1 ≤ 1 liter or ≤ 50% predicted)
- Patients who are on continuous positive inotropic therapy
- Patients with known atrial or ventricular septal defects
- Patients with mechanical right heart valves
- Patients with stenotic tricuspid or pulmonic valves
- Patients with a presently implanted non-compatible pacemaker or ICD
- Patients with cardiac resynchronization therapy which has not, in the opinion of the investigator, achieved optimal programming for more than 3 months
- Patients with a major cardiovascular event (e.g. myocardial infarction, angioplasty, coronary artery bypass grafting) within 3 months prior to baseline evaluation
- Patients with severe non-cardiac condition limiting 6 month survival
- Patients with the primary diagnosis of pulmonary arterial hypertension
- Patients with serum creatinine ≥ 3.5 mg/dL or on chronic renal dialysis
- Patients enrolled in concurrent studies that may confound the results of this study
- Women who are pregnant or with child bearing potential and who are not on a reliable form of birth control

**c. Primary Safety Endpoints**

Safety Objective #1

*Hypothesis:* The freedom from system-related complications at six months is at least 80%.

$H_o$: $P_{\text{(Freedom from system-related complications at 6 months)}} < 80\%$

$H_a$: $P_{\text{(Freedom from system-related complications at 6 months)}} \geq 80\%$

A Chronicle system-related complication is defined as any adverse event that occurs during the clinical investigation, which:

- Is, or is potentially, related to the system (implantable monitor and pressure sensor lead) and at least one of the following:
  - is treated with invasive means,
  - results in the death of the patient,
  - results in the explant of the device,
  - causes a permanent loss of significant function of the system.

Safety Objective #2

*Hypothesis:* The freedom from pressure sensor failure at six months is at least 90%.

$H_o$: $P_{\text{(Freedom from pressure sensor failure at 6 months)}} < 90\%$

$H_a$: $P_{\text{(Freedom from pressure sensor failure at 6 months)}} \geq 90\%$

**d. Primary Effectiveness Endpoint**

*Hypothesis:* The CHRONICLE group will have a significantly lower rate of heart failure related hospital equivalents than the CONTROL group through 6 months,

$H_o$: $\lambda_{\text{CHRONICLE Group}} = \lambda_{\text{CONTROL Group}}$

$H_a$: $\lambda_{\text{CHRONICLE Group}} \neq \lambda_{\text{CONTROL Group}}$

where $\lambda$ is the rate of heart failure related hospital equivalents under an assumption that event rates follow a Poisson distribution.

Hospital equivalents (HE), prospectively defined in the Investigational Plan, included the following events:

1) Heart failure related hospital admissions for 24 hours or longer where the primary reason for admission was worsening heart failure defined as:

- Increased signs and symptoms requiring the administration or augmentation of intravenous (IV) heart failure therapy (diuretics, inotropes, and/or vasodilators);
- Severe dehydration or hypovolemia in the absence of obvious hemorrhagic or gastrointestinal fluid loss; and/or
- Presumed worsening heart failure in the presence of signs and symptoms of heart failure without the requisite therapies (e.g. IV heart failure therapy) to be categorized as worsening heart failure as described above.

2) Heart failure related emergency department visits, which were defined as a visit to the emergency department, which pertain to any of the definitions listed above as heart failure related hospitalizations and necessitates invasive treatment (e.g. IV diuretic administration).

3) Heart failure related (per definitions above) urgent visits, which were defined as a visit to the clinic which was not scheduled, occurs on the same day the patient communicated distress and necessitated invasive treatment (e.g. IV diuretic administration).

**e. Secondary Endpoints**

There were no pre-specified performance criteria related to the secondary objectives in the COMPASS-HF study. Secondary endpoints included the following:

- Health care utilization
- Days alive out of the hospital
- Patient survival
- Rate of adverse events
- Predictive value of pressure change in the CONTROL group
- Composite response endpoint
- Quality of life
- New York Heart Association (NYHA) Functional Class
- Distance walked in six minutes

Please refer to the Clinical Experience portion of the panel pack, prepared by the sponsor, for a detailed discussion of results for the various secondary endpoints in this study.

**f. Results – Primary Safety Endpoints**

Safety objective #1

*Hypothesis:* The freedom from system-related complications must be significantly greater than 80% at 6 months.

This analysis was conducted on ALL subjects who were implanted (or had an attempted implant) with the Chronicle system. Per the Chronicle Events Committee (CEC) adjudication, there were a total of 24 system-related complications in 23 patients that occurred from the 277 patients with an implant attempt.

The following tables have been copied from the sponsor's pre-market approval (PMA) application.

| Primary Diagnosis | Number of Events CHRONICLE (patients) | Number of Events CONTROL (patients) | Total (patients) |
|---|---|---|---|
| Lead dislodgement | 7 (7) | 8 (7) | 15 (14) |
| Lead body damage | 1 (1) | 1 (1) | 2 (2) |
| Artifact on waveform | 1 (1) | 3 (3) | 4 (4) |
| Lead Migration# | 1 (1) | 0 (0) | 1 (1) |
| Entrapped Lead in Tricuspid Valve# | 0 (0) | 0 (0) | 1 (1) |
| Premature battery failure | 0 (0) | 1 (1) | 1 (1) |
| **Total** | **10 (10)** | **13 (12)** | **24 (23)** |

# classified as Other by clinician and further classified by Medtronic.

^ Patient not randomized, event occurred during unsuccessful implant.

| | Number of Patients with Attempted Implant | Number of Complications (patients) | Freedom from System Complication | Lower 1-sided 95.10% Confidence Interval |
|---|---|---|---|---|
| Final Analysis | 277 | 24 (23) | 91.5% | 88.7% |

The freedom from system related complications rate through 6 months was 91.5% with a lower one-sided 95.10% confidence bound of 88.7% which is above the predetermined performance criterion of 80%. The objective was met.

Safety objective #2

*Hypothesis:* The freedom from pressure sensor failure at six months is at least 90%.

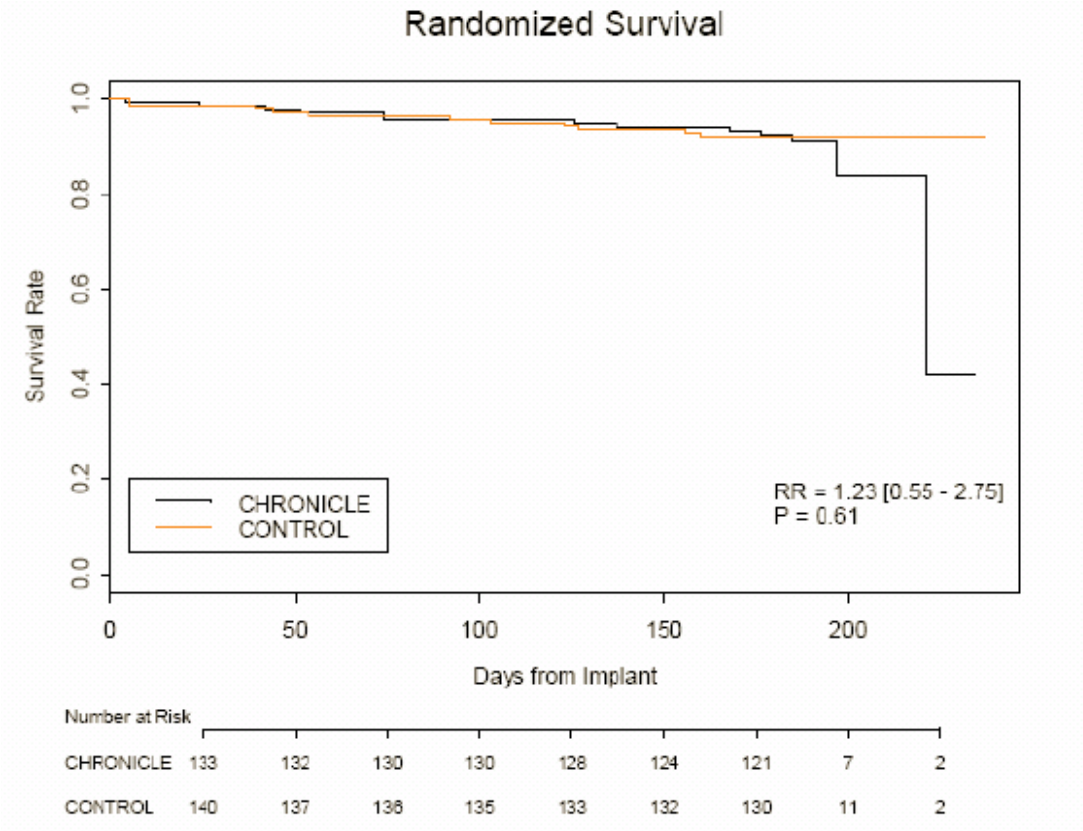
There were a total of 0 pressure sensor failures that occurred in the 274 successfully implanted and randomized patients. The freedom from failure rate through 6 months was 100% with a lower one-sided 95.10% confidence interval of 98.9%, which is above the predetermined objective of 90%. The objective was met.

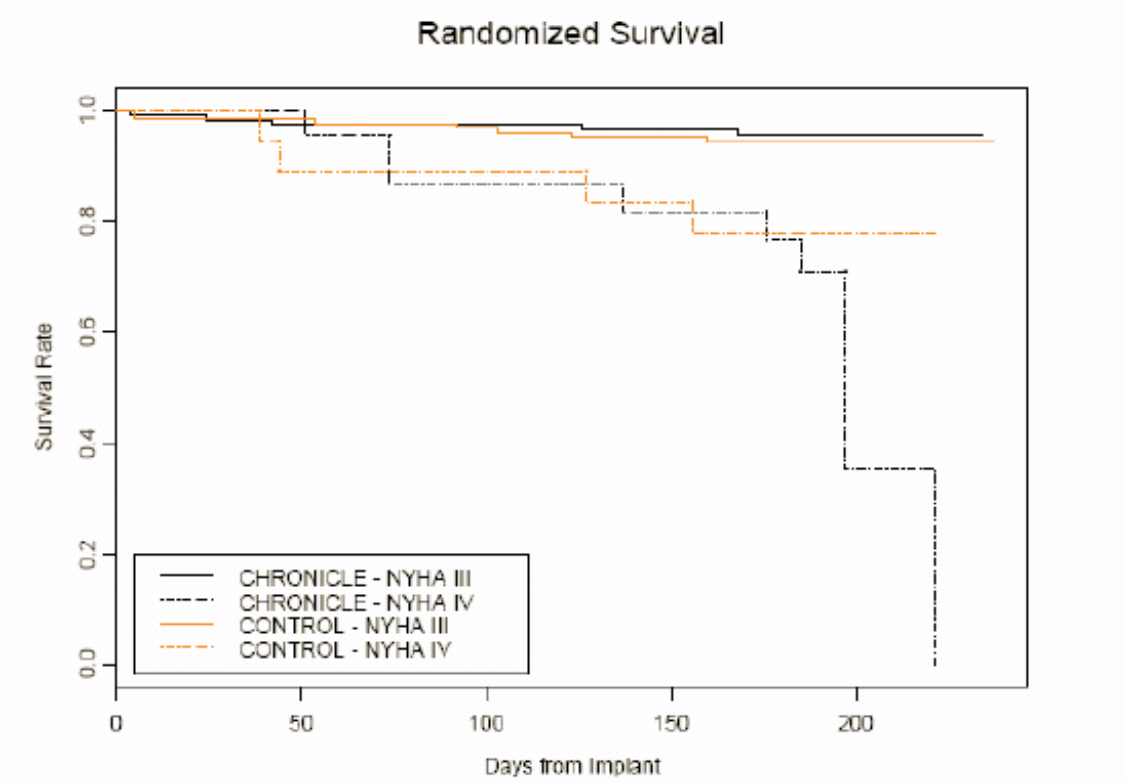
**g. Survival Analysis**

FDA feels that it is important to point out the results of the survival analysis included in the PMA. Each death was reviewed individually by the FDA review team. The deaths were largely due to expected causes such as progressive heart failure and sudden cardiac death. Less common causes of death included sepsis/infection and renal failure. The overall mortality rates seen in the COMPASS-HF trial were similar to the mortality rates

reported in the control arm of studies with similar patient populations (NYHA Class III/IV heart failure and severe left ventricular systolic dysfunction).

Based on the two graphs below, which portray survival curves for the randomized period, it appears there is a slight trend toward reduced survival in the Chronicle group (due mostly to NYHA Class IV patients). However, FDA also acknowledges the small number of patients contributing to the long-term evaluation.






**h. Results – Primary Effectiveness Endpoint**

*Hypothesis:* The CHRONICLE group will have a significantly lower rate of heart failure related hospital equivalents than the CONTROL group through 6 months.

There were a total of 472 reported all-cause visits to the hospital, emergency department (ED) or urgent clinic. The CEC classified 197 of the 472 total events as HF-related hospital equivalents.

Using the CEC classification, overall, 44 patients (33%) in the CHRONICLE group and 60 patients (43%) in the CONTROL group experienced 84 and 113 HF-related hospital equivalents, respectively, during the randomized follow-up period. This resulted in an event rate of 0.67 and 0.85 for the CHRONICLE and CONTROL patients, respectively – an absolute reduction of 0.18 hospital equivalents per patient per 6 months. This 21% reduction in overall HF-related hospital equivalents was not statistically significant, with a p-value of 0.33 using the Negative Binomial Regression technique. These results are presented in the table below.

In summary, the pre-specified primary effectiveness endpoint was not met.

| | CHRONICLE (n=134) | CONTROL (n=140) |
|---|---|---|
| **# of Patients with Events** | **44** | **60** |
| **Total Hospital Equivalents** | **84** | **113** |
| Hospitalizations | 72 | 99 |
| Emergency Department Visits | 10 | 11 |
| Urgent Clinic Visits | 2 | 3 |
| **Months at Risk** | **752** | **795** |
| **Event Rate / 6 months** | **0.67** | **0.85** |
| **% Reduction in Event Rate** | **21% (p=0.33)** | |

**i. Subgroup Analyses of Primary Effectiveness Endpoint**

A pre-specified sub-group analysis illustrated that impact of IHM Guided Care was consistent across several sub-groups, except NYHA Class. While the interaction p-value for NYHA Class was not significant (p=0.08), because there was a directional difference in the response to IHM Guided Care between NYHA Class III and IV patients, additional analyses were conducted to examine this differential effect.

*Note:* Alpha was not pre-specified for these analyses, making it difficult to interpret the significance of any p-values.

NYHA Class III

In NYHA Class III subjects, 35 patients in the CHRONICLE group and 51 patients in the CONTROL group experienced 58 and 99 HF-related hospital equivalents, respectively, during the randomized follow-up period. This resulted in an event rate of 0.54 and 0.85 for the CHRONICLE and CONTROL patients, respectively – an absolute reduction of 0.31 hospital equivalents per patient per 6 months. This 36% reduction in overall HF-related hospital equivalents resulted in a p-value of 0.058 using the Negative Binomial Regression technique.

The table below (submitted in the PMA) provides a summary of the primary endpoint events that occurred in NYHA Class III patients.

| Type of Visit | CHRONICLE | CONTROL |
|---|---|---|
| ED | 3 | 11 |
| Urgent Visit | 2 | 3 |
| < 24-Hour Hospital Stay | 3 | 0 |
| Hospital Admission | 50 | 85 |
| Total Events | 58 | 99 |
| Number of Patients with Events | 35 | 51 |

NYHA Class IV

In NYHA Class IV subjects, 9 patients in the CHRONICLE group and 9 patients in the CONTROL group experienced 26 and 14 HF-related hospital equivalents, respectively, during the randomized follow-up period. This resulted in an event rate of 1.44 and 0.89 for the CHRONICLE and CONTROL patients, respectively – an absolute *increase* of 0.55 hospital equivalents per patient per 6 months. This 62% increase in overall HF-related hospital equivalents resulted in a p-value of 0.27 using the Negative Binomial Regression technique.

The table below (submitted in the PMA) provides a summary of the primary endpoint events that occurred in NYHA Class IV patients.

| Type of Visit | CHRONICLE | CONTROL |
|---|---|---|
| ED | 2 | 0 |
| Urgent Visit | 0 | 0 |
| < 24-Hour Hospital Stay | 2 | 0 |
| Hospital Admission | 22 | 14 |
| Total Events | 26 | 14 |
| Number of Patients with Events | 9 | 9 |

In the PMA, the sponsor performed *post* hoc analyses to assess whether the NYHA Class IV subjects randomized to the Chronicle arm of the trial were actually sicker than the

NYHA Class IV subjects randomized to the Control arm of the trial. Differences in the Class IV subjects included the following:

- 12/22 (54%) CHRONICLE patients had a six minute hall walk distance of ≤ 100 meters compared to 3/18 (17%) in the CONTROL group.

- 11/22 (50%) CHRONICLE patients had a baseline creatinine of > 1.9 mg/dL compared to 0 patients in the CONTROL group.

- 15/22 (68%) CHRONICLE patients had a Minnesota Living with Heart Failure (MLHF) score of > 80 compared to 7/18 (39%) in the CONTROL group.

Based on these findings, the sponsor examined several other baseline characteristics of patients enrolled in the trial to determine which covariates may have had added influence on the primary endpoint outcome. These *post hoc* analyses are discussed in the next section.

**j. *Post Hoc* Effectiveness Analyses**

Further analysis illustrated that there were small, yet potentially important imbalances between the two study groups (CHRONICLE and CONTROL) with respect to several baseline clinical characteristics that were associated with the primary outcome measure in the study. The sponsor hypothesized that controlling for these baseline clinical characteristics in all study patients may reveal the true effect of Chronicle Guided Care. To adjust for the influence of these significant predictive characteristics on the primary endpoint of the study, a multivariable methodology was implemented.

This section presents the results from *post hoc* analyses of the effectiveness of the Chronicle IHM System based on a multivariable adjustment for prognostic baseline covariates and specific imbalances observed in the COMPASS-HF data set. 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); and
- Relative risk of death or heart failure-related hospitalization (CHRONICLE vs. CONTROL).

To adjust for the influence of these predictive characteristics on the primary endpoint of the study, a multivariable methodology was implemented. Those characteristics that emerged as 'significantly' related to the primary endpoint ($p \leq 0.05$) were then included

in a multivariable negative binomial or Cox proportional hazard regression model along with the treatment group covariate.

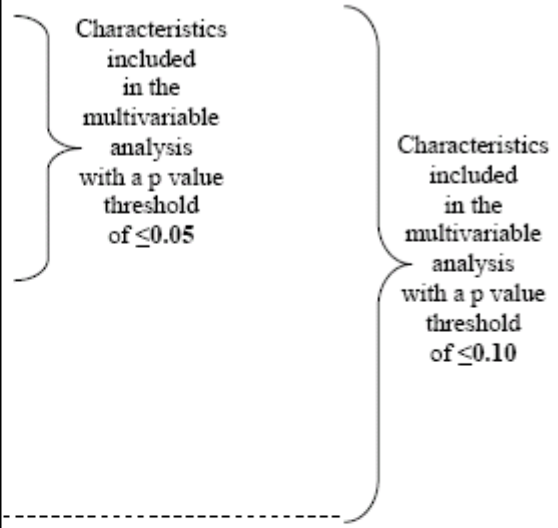
After an initial review of these *post hoc* analyses, FDA felt that including only those covariates with a $p \leq 0.05$ might exclude potentially clinically relevant concomitant variables. Therefore, we requested that the sponsor perform additional analyses that include all identified covariates of $p \leq 0.10$ in the model in an effort to provide a more conservative and informative analysis.

These steps were applied to each of the five *post hoc* effectiveness analyses mentioned previously. For each endpoint, the results of the univariate analysis depicting the relationship between all tested baseline characteristics and outcome are presented. In addition, those clinical characteristics that were included in the originally reported multivariable analysis ($p \leq 0.05$) as well as those that have been included in the additional analysis requested by FDA ($p \leq 0.10$) are highlighted. Then, the results of the estimated treatment effect using the unadjusted and the two *post hoc* adjusted analyses are presented. These tables were all included in the sponsor's PMA.

*Note:* All analyses using this adjustment methodology were conducted *post hoc*. Therefore, interpretation of results, especially the significance of p-values, may be difficult.

Reduction in HF-Related Hospital Equivalent

| Baseline Characteristic | P Value |
|---|---|
| Number of Prior HF Events | 0.0002 |
| 6-Minute Hall Walk | 0.0003 |
| Atrial Fibrillation | 0.0004 |
| Quality of Life (MN Living with Heart Failure Score) | 0.0012 |
| Creatinine | 0.0019 |
| ACE/ARB at Baseline | 0.0377 |
| Concomitant Device | 0.0479 |
| Rales | 0.06 |
| NYHA Class | 0.07 |
| LVEF | 0.07 |
| Beta Blocker at Baseline | 0.07 |
| QRS Duration | 0.07 |
| Diabetes | 0.08 |
| Toprol XL Dose | 0.09 |
| Etiology (Ischemic vs. Non-Ischemic) | 0.11 |
| JVP | 0.13 |
| Hemoglobin | 0.16 |
| Age | 0.21 |
| Gender | 0.27 |
| Enalapril Dose | 0.28 |
| Spironolactone Dose | 0.33 |
| Sodium | 0.34 |
| Diastolic/Systolic HF | 0.35 |
| Diuretic at Baseline | 0.62 |
| Years Diagnosed with HF | 0.64 |
| Carvedilol Dose | 0.75 |
| Systolic BP | 0.94 |




| | Reduction in HF-Related Hospital Equivalent Event Rate (95% CI) | P Value |
|---|---|---|
| **Unadjusted Model**<br>Volume 21, Section IX: Results: Primary Efficacy Objective, Page 7447 | 21%<br>(-25%-48%) | 0.33 |
| **Adjusted Model including covariates ≤ 0.05**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 2, Page 6 | 28%<br>(-8%-52%) | 0.11 |
| **Adjusted Model including covariates ≤ 0.10** | 23%<br>(-16% - 48%) | 0.21 |

*Note:* This was the protocol-specified primary endpoint. However, the adjusted analyses were conducted *post hoc.*

Relative Risk Reduction of HF-Related Hospital Equivalent

| Baseline Characteristic | P Value |
|---|---|
| Rales | 0.0006 |
| 6-Minute Hall Walk | 0.0009 |
| Number of Prior HF Events | 0.0012 |
| ACE/ARB at Baseline | 0.0012 |
| Creatinine | 0.0013 |
| Etiology (Ischemic vs. Non-Ischemic) | 0.0024 |
| Quality of Life (MN Living with HF score) | 0.0055 |
| Atrial Fibrillation | 0.0089 |
| QRS Duration | 0.0394 |
| Age | 0.07 |
| Beta Blocker at Baseline | 0.07 |
| Concomitant Device | 0.07 |
| Diabetes | 0.08 |
| LVEF | 0.09 |
| Toprol XL Dose | 0.12 |
| Hemoglobin | 0.16 |
| Sodium | 0.18 |
| JVP | 0.20 |
| NYHA Class | 0.21 |
| Spironolactone Dose | 0.38 |
| Carvedilol Dose | 0.55 |
| Diastolic/Systolic HF | 0.59 |
| Gender | 0.63 |
| Enalapril Dose | 0.68 |
| Diuretic at Baseline | 0.74 |
| Systolic BP | 0.91 |
| Years Diagnosed with HF | 0.97 |

Characteristics included in the multivariable analysis with a p value threshold of ≤0.05

Characteristics included in the multivariable analysis with a p value threshold of ≤0.10

| | Relative Risk Reduction (Hazard Ratio, 95% CI) | P Value |
|---|---|---|
| **Unadjusted Model**<br>Volume 21, Section IX: Results: Primary Efficacy Objective, Page 7450 | 27%<br>(0.73, 0.49-1.07) | p=0.10 |
| **Adjusted Model including covariates ≤ 0.05**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 5, Page 9 | 38%<br>(0.62, 0.41-0.94) | p=0.0227 |
| **Adjusted Model including covariates ≤ 0.10** | 40%<br>(0.60, 0.40-0.92) | p=0.0184 |

*Note:* This was pre-specified as an alternative analysis of the primary endpoint. Alpha was not prospectively assigned to the unadjusted analysis. The adjusted analyses were *post hoc*.

Relative Risk Reduction of All-Cause Death or HF-Related Hospital Equivalent

| Baseline Characteristic | P Value |
|---|---|
| Creatinine | 0.0003 |
| Number of Prior HF Events | 0.0003 |
| 6-Minute Hall Walk | 0.0009 |
| Rales | 0.0011 |
| ACE/ARB at Baseline | 0.0022 |
| Etiology (Ischemic vs. Non-Ischemic) | 0.0034 |
| Quality of Life (MN Living with HF score) | 0.0069 |
| QRS Duration | 0.0112 |
| Atrial Fibrillation | 0.0117 |
| NYHA Class | 0.0146 |
| Age | 0.0212 |
| Beta Blocker at baseline | 0.0408 |
| LVEF | 0.06 |
| Sodium | 0.06 |
| Hemoglobin | 0.06 |
| Toprol XL Dose | 0.11 |
| Concomitant Device | 0.13 |
| JVP | 0.16 |
| Diabetes | 0.26 |
| Diastolic/Systolic HF | 0.37 |
| Systolic BP | 0.44 |
| Enalapril Dose | 0.48 |
| Carvedilol Dose | 0.49 |
| Spironolactone Dose | 0.49 |
| Diuretic at Baseline | 0.59 |
| Years Diagnosed with HF | 0.83 |
| Gender | 0.87 |

Characteristics included in the multivariable analysis with a p value threshold of ≤0.05

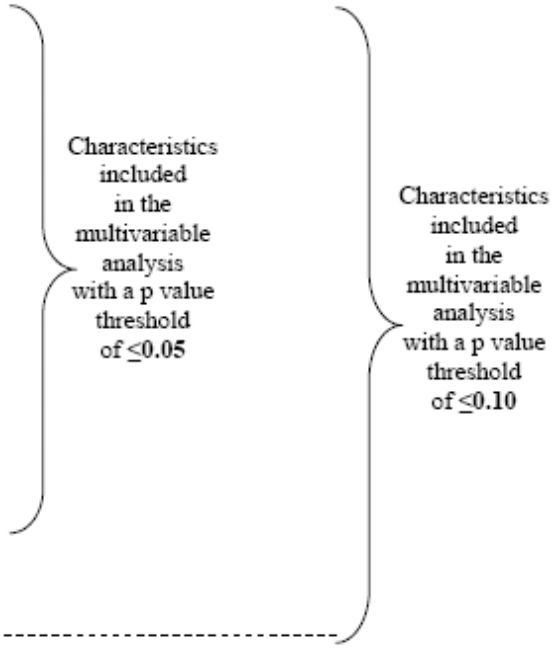
Characteristics included in the multivariable analysis with a p value threshold of ≤0.10

| | Relative Risk Reduction (Hazard Ratio, 95% CI) | P Value |
|---|---|---|
| **Unadjusted Model**<br>PMA Amendment (April 18, 2006), Part 1 Deficiency Question 1, Table 8, Page 12 | 23%<br>(0.77, 0.53-1.10) | P=0.15 |
| **Adjusted Model including covariates ≤ 0.05**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 8, Page 12 | 34%<br>(0.66, 0.45-0.97) | P=0.0349 |
| **Adjusted Model including covariates ≤ 0.10** | 32%<br>(0.68, 0.46-1.01) | P=0.0554 |

*Note:* All analyses for this endpoint were conducted *post hoc*.

Relative Risk Reduction of All-Cause Death or HF-Related Hospitalization

| Baseline Characteristic | P Value |
|---|---|
| Creatinine | <0.0001 |
| 6-Minute Hall Walk | 0.0004 |
| Rales | 0.0007 |
| ACE/ARB at Baseline | 0.0009 |
| NYHA Class | 0.0037 |
| Etiology (Ischemic vs. Non-Ischemic) | 0.0043 |
| Quality of Life (MN Living with Heart Failure Score) | 0.0078 |
| QRS Duration | 0.0078 |
| Number of Prior HF Events | 0.0100 |
| Atrial Fibrillation | 0.0106 |
| Age | 0.0139 |
| Hemoglobin | 0.0210 |
| LVEF | 0.0236 |
| Sodium | 0.0316 |
| Toprol XL Dose | 0.07 |
| Concomitant Device | 0.08 |
| JVP | 0.10 |
| Diastolic/Systolic HF | 0.16 |
| Beta Blocker at Baseline | 0.17 |
| Diabetes | 0.32 |
| Systolic BP | 0.46 |
| Carvedilol Dose | 0.52 |
| Enalapril Dose | 0.63 |
| Years Diagnosed with HF | 0.66 |
| Diuretic at Baseline | 0.70 |
| Spironolactone Dose | 0.76 |
| Gender | 0.88 |




| | Relative Risk Reduction (Hazard Ratio, 95% CI) | P Value |
|---|---|---|
| **Unadjusted Model**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 11, Page 15 | 28%<br>(0.72, 0.49-1.05) | P=0.08 |
| **Adjusted Model including covariates ≤ 0.05**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 11, Page 15 | 35%<br>(0.65, 0.43-0.97) | P=0.0346 |
| **Adjusted Model including covariates ≤ 0.10** | 33%<br>(0.67, 0.44-1.001) | P=0.0504 |

*Note:* All analyses for this endpoint were conducted *post hoc*.

Relative Risk Reduction of HF-Related Hospitalization

| Baseline Characteristic | P Value |
|---|---|
| Rales | 0.0002 |
| 6-Minute Hall Walk | 0.0012 |
| Creatinine | 0.0016 |
| ACE/ARB at Baseline | 0.0022 |
| Etiology (Ischemic vs. Non-Ischemic) | 0.0056 |
| Quality of Life (MN Living with HF Score) | 0.0083 |
| Atrial Fibrillation | 0.0156 |
| Number of Prior HF Events | 0.0439 |
| Hemoglobin | 0.0482 |
| Age | 0.054 |
| QRS Duration | 0.06 |
| LVEF | 0.06 |
| Concomitant Device | 0.07 |
| Toprol XL Dose | 0.09 |
| Sodium | 0.13 |
| JVP | 0.14 |
| Diabetes | 0.15 |
| Beta Blocker at Baseline | 0.23 |
| NYHA Class | 0.23 |
| Diastolic/Systolic HF | 0.34 |
| Spironolactone Dose | 0.53 |
| Years Diagnosed with HF | 0.76 |
| Carvedilol Dose | 0.78 |
| Diuretic at Baseline | 0.90 |
| Enalapril Dose | 0.92 |
| Systolic BP | 0.93 |
| Gender | 0.98 |

Characteristics included in the multivariable analysis with a p value threshold of ≤0.05

Characteristics included in the multivariable analysis with a p value threshold of ≤0.10

| | Relative Risk Reduction (Hazard Ratio, 95% CI) | P Value |
|---|---|---|
| **Unadjusted Model**<br>Volume 21, Section IX: Results: Primary Efficacy Objective, Page 7451 | 36%<br>(0.64, 0.42-0.96) | P=0.03 |
| **Adjusted Model including covariates ≤ 0.05**<br>PMA Amendment (April 18, 2006) Part 1, Deficiency Question 1, Table 14, Page 18 | 42%<br>(0.58, 0.38-0.89) | P=0.0137 |
| **Adjusted Model including covariates ≤ 0.10** | 43%<br>(0.57, 0.37-0.89) | P=0.0133 |

*Note:* All analyses for this endpoint were conducted *post hoc*.

In the Clinical Experience section of their panel pack, the sponsor has provided a rationale for using the multivariable adjustment methodology to potentially obtain a better estimate of the treatment effect as evaluated within the setting of a controlled randomized clinical trial.

While it is true that precedent exists in the statistical literature for applying analysis of covariance techniques after the data has been collected due to some bias that may have entered the study despite attempts at randomization, there are a number of cautions and qualifiers that accompany such analyses.

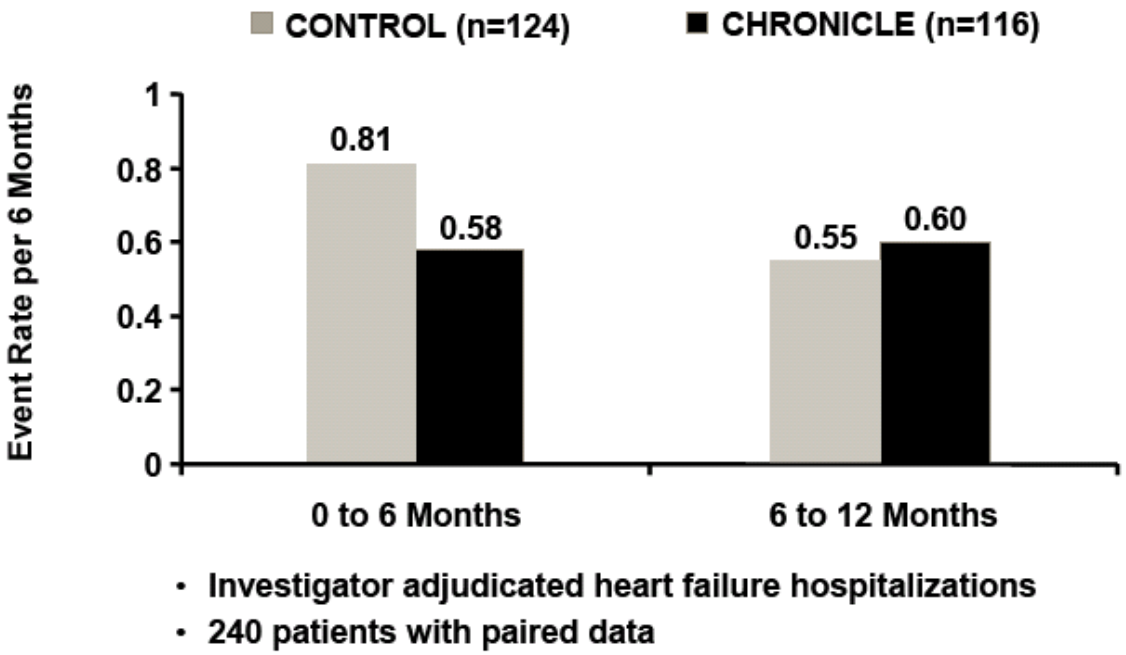
It is clear from the same literature cited by the sponsor,[1,2] and other widely accepted texts,[3] that all interpretations of such *post hoc* analyses must be made with caution. First, it is important to note that the use of a covariate plan is most appropriate when established *a priori*. Although some bias may not have been evident during the randomization stage, having a general strategy in place *a priori* to identify some potential concomitant variables for a potential ANCOVA would have been ideal. This was not done here, even though the strategy is recommended in the Pocock article,[1] and in other clinical trial texts.

Further, the Pocock review of trials[1] reports that in only one case did the adjusted model change the results – and it is noted that it is rare in general practice. That the results have changed here as a result of an adjusted model, and then changed again after modifying the model to the 0.10 level, provides further reason to be cautious in the statistical interpretation of these new results. The length of time in this analysis may not be what would be considered long-term results as noted in the Ford and Norrie paper.[2]

**k. Durability of Treatment Effect**

The sponsor also assessed the impact of Chronicle Guided Care beyond the six-month randomization period, when access to the IHM data was enabled for all study participants. This analysis included the 240 patients for whom paired data was available from both the six-month randomization period and the subsequent six months. Only heart failure hospitalizations, which comprised a majority of the heart failure equivalent events during the randomized portion of the study, were examined in this analysis. All events in this analysis are based on investigator adjudication. Event rates were defined as the ratio of the number of events by the total number of months at risk.

As seen in the graph below, event rates in the CHRONICLE group were consistent in both time periods (0.58 and 0.60); in addition, once IHM data became available for the management of CONTROL patients, their event rate declined from 0.81 during the randomized follow-up period to 0.55, a rate similar to that observed in the CHRONICLE group. These two findings suggest that Chronicle Guided Care may lead to a consistent effect on heart failure hospitalizations.




## 6. POST-APPROVAL STUDY

The FDA review team, which includes an epidemiologist, has made the recommendation that if the Chronicle IHM System is approved, a post-approval study should be conducted as a condition of approval for this first-of-a-kind device. Throughout our review of the PMA, FDA and the sponsor have worked closely to design this potential study. Please refer to the sponsor's portion of the panel pack, where an overview of the post-approval study design is provided.

*Note:* We would like to remind you that the presence or content of a post-approval study is not a substitute for the requirement of demonstrating a reasonable assurance of safety and effectiveness prior to pre-market approval. Therefore, the post-approval study will only be discussed during the Advisory Panel meeting if the Panel recommends Approval or Approvable with Conditions.

## 7. REFERENCES

1. Pocock, S.J., et al. Subgroup analysis, covariate adjustment and baseline comparisons in clinical reporting: current practice and problems. Stat. in Medicine 2002:21:2917-2930.

2. Ford I., and Norrie, J. The Role of Covariates in Estimating Treatment Effects and Risk in long term Clinical Trials. Stat. in Medicine 2002:21:2899-2908.

3. Friedman, L.M., Furberg, C.D., and DeMets, D.L. (1999). Fundamentals of Clinical Trials. 3rd Ed. Springer-Verlag, New York.