VOLUME 1

SECTION 4:
EXECUTIVE SUMMARY

Executive Summary

1. Background

The treatment of patients with heart failure has improved dramatically over the last two decades. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and more recently cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs), have all been shown to improve patient outcomes.[1–11] Yet, despite this progress, the number of hospitalizations for worsening heart failure continues to rise.[12]

The majority of hospitalizations for acute decompensated heart failure are due to the accumulation of fluid and the accompanying increase in filling pressures.[13] The relationship between increased filling pressures and congestive signs and symptoms is well established in the acute setting, where therapy resulting in the reduction of these pressures is associated with improvement in both symptoms and cardiac function.[14] Monitoring changes in patients' volume status is an important component of the current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the management of chronic heart failure.[15] However, current methods for assessing volume, such as physical examination, chest radiography, and daily weights often correlate poorly with true volume status in patients with chronic heart failure.[16-18] Even when fluid status is correctly assessed in the clinic, meaningful changes often occur between visits, in the ambulatory setting, where reliable information pertaining to volume status is lacking. Thus, early signs of decompensation are often missed, along with the opportunity for timely intervention.

During hospitalization, right heart pressures obtained from pulmonary artery catheterization may be used to guide heart failure treatment. However, such catheterization is invasive, provides only a static assessment of a dynamic state, and is practically limited to the inpatient setting. Importantly, the initial benefits of such monitoring in improving renal function and mitral regurgitation are lost as clinical conditions change after discontinuation of monitoring.[19-21]

Given the difficulty of accurately assessing congestion in the outpatient setting as well as the emerging evidence linking volume overload and congestion with an increased risk of hospitalization, it was envisioned that the Chronicle Implantable Hemodynamic Monitor (IHM) would offer a novel physiological approach to identify the early signs of worsening heart failure and reduce the risk of hospitalization. Reducing heart failure-related hospitalizations is important not only because of quality of life concerns and surging healthcare costs, but also because of the growing body of evidence suggesting that once hospitalized with symptoms of congestion, heart failure patients often receive high doses of diuretics and other therapies that may actually be deleterious and worsen long-term outcomes.[22]

The Chronicle IHM system was developed to provide clinicians with the ability to accurately and reliably assess intracardiac pressures as indicators of volume status in ambulatory heart failure patients.

2. Chronicle IHM System Description

The Chronicle IHM (IHM herein) system continuously measures and records numerous physiological parameters, including heart rate, core temperature, patient activity, right ventricular pressures, and estimated pulmonary artery diastolic pressure (an indicator of left ventricular filling pressure). Clinicians can access data recorded by the IHM by either directly interrogating the device in the office setting or via a secure Web site that stores information transmitted by the patient remotely.

The Chronicle IHM system includes both implantable and external components:

- Implantable components:
  - Hemodynamic monitor – a battery-powered monitoring and data storage device, similar in size and shape to a pacemaker that is implanted in the pectoral region.
  - Pressure sensing lead – a transvenous, non-pacing lead that is positioned in the right ventricular outflow tract. It has both electrogram and pressure sensing capabilities.

- External components:
  - External pressure reference (EPR) – a pager-sized, battery-powered device that is carried by the patient to continuously measure barometric pressure.
  - Remote monitor – a battery-powered transmission device, typically located in the patient's home that simultaneously interrogates the IHM and the EPR and then transmits the stored data over a standard phone line to a secure remote server.
  - Chronicle IHM Web site – a secure password-protected Web-based application that analyzes, stores, and displays pressure information. The Web site is intended for remote review of data by clinicians using a standard Internet browser.
  - Programmer – a clinic-based computer that can be used to both program and interrogate the IHM.

3. Clinical Experience with the Chronicle IHM System

This summary presents clinical evidence with the Chronicle IHM system in 422 patients, with an aggregate follow-up of over 700 patient-years since 1998. Two main studies, the Chronicle Phase I & II Study (n=148 patients) and COMPASS-HF (n=274 patients), are discussed in this summary.

4. Accuracy, Reliability and Safety of the Chronicle IHM System

The Chronicle IHM Phase I & II study was a multi-center, prospective, non-randomized trial to establish the accuracy, reliability, and safety of the Chronicle IHM system.

Phase I focused on establishing the accuracy of the measurements taken by the IHM. With 32 patients serving as their own control, paired right ventricular pressure measurements were taken simultaneously with the IHM and a Swan-Ganz catheter during supine rest, Valsalva maneuver, sitting rest, and bicycle exercise testing. Measurements were obtained at the time of IHM implant and at the three-, six-, and twelve-month follow-up visits. Overall, strong correlations were found between the Chronicle IHM and the Swan Ganz catheter across all measured pressure parameters (0.96 and 0.94 for right ventricular (RV) systolic pressure, 0.96 and 0.83 for RV

diastolic pressure, and 0.87 and 0.87 for estimated pulmonary artery diastolic pressure (ePAD) at implant and one year, respectively), with minimal drift up to one year post IHM implant.[23]

Phase II focused on further assessing the safety and reliability of the Chronicle IHM system and on gaining experience with the clinical utility of the device. Therefore, the additional 116 patients enrolled in Phase II were not required to undergo Swan-Ganz catheterization. These patients were followed monthly through four months, and then every other month through twelve months. Thereafter, patients entered a long-term follow-up schedule of every six months until market approval.

Severe IHM-related adverse events, IHM-related complications, and pressure sensor reliability were all evaluated using data from the 148 enrolled Phase I & II patients. Both freedom from severe IHM-related adverse events and IHM-related complications met the study's stated objectives. However, a number of pressure sensor failures were encountered in specific manufacturing lots during the study. The root cause was identified and subsequently corrected, with no further occurrences.

During Phase II, a group of clinical investigators 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.[24] 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 ACC/AHA guidelines was recommended. This strategy, termed IHM Guided Care, was subsequently tested in the latter stages of the Phase I & II study and in COMPASS-HF.

To assess the potential clinical utility of the Chronicle IHM, the records of Phase I patients were reviewed for the occurrence of heart failure-related hospitalizations. This analysis revealed 1.08 hospitalizations per patient-year of follow-up prior to the use of IHM data to support clinical decision making. In contrast, during a 17-month period when IHM data were available to support clinical care, the hospitalization rate was 0.47 per patient-year. This represented a 57% reduction in the rate of heart failure hospitalizations ($p<0.01$).[25]

A further analysis of records from 67 patients enrolled in Phase I & II revealed a 53% reduction in hospitalizations during six months of IHM Guided Care compared to six months without IHM Guided Care ($p=0.05$).[26]

Although these retrospective analyses were performed on small non-randomized samples, their results provided additional support for the potential value of IHM Guided Care in reducing heart failure hospitalizations and set the stage for the design of the COMPASS-HF study.

5. COMPASS-HF

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-guided management strategy in patients with advanced heart failure who were already receiving standard medical care. The primary objectives of the study were to further evaluate the safety of the IHM system and to determine the effectiveness of an ambulatory, remote patient management strategy based on continuously monitored intracardiac pressures in reducing patient morbidity. Morbidity was measured by a composite of heart failure-related events (hospitalizations, emergency department visits, and urgent clinic visits requiring intravenous therapy for heart failure).

COMPASS-HF 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 heart failure outcome measure that was intended to include not only the recognized endpoint of hospitalizations, but also urgent visits that might be increased due to physician concern about abnormal hemodynamic data reported by the Chronicle IHM.
- To evaluate the difference in this composite effectiveness endpoint, the study pre-specified an analytical methodology to test the difference in event rates as opposed to using the traditional relative risk or time-to-first-event methodology (Cox regression).
- All patients in COMPASS-HF received a Chronicle IHM; however, none of the CONTROL patients were managed using information from the IHM until their six-month randomized follow-up visit was completed.
- Meticulous attention was paid to the CONTROL group in order to keep the patients blind to their management strategy (with or without Chronicle IHM). As a result of this design safeguard, CONTROL patients were frequently contacted to match the intensive communication observed in the CHRONICLE group.
- Only centers with well established and dedicated heart failure programs were considered for participation in the COMPASS-HF study. Participating centers were selected based on their comprehensive approach to heart failure care.

- The study 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. As a result, the study was stratified by baseline ejection fraction with no pre-specified hypothesis associated with this criterion.

COMPASS-HF enrolled patients with NYHA Class III or IV heart failure who were either hospitalized for worsening heart failure or received IV therapy for heart failure in an emergency department during the six months prior to study enrollment. All patients had to be on standard medical therapy as tolerated (beta-blocker, ACE inhibitor/ARB and diuretics) for at least three months prior to enrollment. Patients with a CRT or CRT-defibrillation system were allowed to participate as long as they met the above criteria and their device was optimally programmed (as defined by the study investigator) for at least three months prior to enrollment.

Of the 277 patients who underwent a Chronicle IHM implant attempt, 274 patients were successfully implanted and randomized to either the CHRONICLE arm (managed using standard heart failure medical care in conjunction with IHM Guided Care, n=134) or the CONTROL arm (managed using standard heart failure medical care alone, n=140). Randomization was stratified by ejection fraction (<50% vs. ≥50%), and the randomized follow-up period was six months.

Pre-Specified Primary Safety Endpoints

It was hypothesized that at six months, the freedom from system-related complications would be greater than or equal to 80%, and the freedom from pressure sensor failures would be greater than or equal to 90%. Both safety endpoints of the study met their pre-specified performance criteria, demonstrating an acceptable system safety profile. Notably, there were no pressure sensor failures in the COMPASS-HF study.

Pre-Specified Primary Effectiveness Endpoint

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.

Two key assumptions were made in estimating the sample size requirements of COMPASS-HF that may have affected the ability of the study to meet its primary effectiveness endpoint:

1) **Average CONTROL event rate would be 1.2 per six months.**

   The observed average event rate in COMPASS-HF was 0.85 per six months, lower than anticipated and likely reflecting in part the diligent efforts to maintain blinding in the CONTROL group by matching the intensive rate of patient contact 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 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. 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 hospitalizations[27-28], 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 distribution[29], 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 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) that likely hindered the ability of the trial to meet its primary endpoint.

Post-hoc Analyses

- The traditional endpoint of relative risk of a heart failure hospitalization showed a clear benefit in favor of IHM Guided Care. One-hundred seventy-one (171) out of the 197 (87%) heart failure events that contributed to the primary endpoint were heart failure hospitalizations. A post-hoc time-to-first-event analysis demonstrated a 36% reduction in the relative risk of a heart failure-related hospitalization, with a p-value of 0.03.
- The impact of IHM Guided Care was consistent in patients with a preserved ejection fraction (20% reduction in event rate, p-value not significant, comparable to the 21% reduction observed in the complete study cohort).
- The COMPASS-HF study confirmed the underlying physiologic principles on which this volume management strategy is based:
    - Increased filling pressures lead to events: Patients enrolled in the COMPASS-HF study sustained a consistent and significant increase in intracardiac pressures in the days and weeks preceding admission for symptomatic decompensation.
    - Filling pressures are not reliably reflected by body weight: Analysis of body weight and right ventricular diastolic pressure prior to and following admission for heart failure-related hypervolemia demonstrated that while pressures consistently increased in the days leading to admission, body weight changed minimally in the same time frame. This observation indicates that measurement of intracardiac pressures is more sensitive in the detection of pending decompensations, although rapid weight gain in the days leading to an event may be highly specific.
    - Appropriate interventions were made when filling pressure information was available: 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 attributable to diuretics, which were adjusted 53% more often using the IHM information in the CHRONICLE group ($p<0.001$). Furthermore, because filling pressures were monitored after intervention, there was no signal of increased episodes of hypovolemia or renal dysfunction. There was no increase in adverse events in the CHRONICLE arm that might be attributed to the excessive use of diuretics (e.g. dehydration or worsening renal function).
- After completion of their blinded six-month randomized follow-up period, patients in the CONTROL group were also managed using IHM Guided Care. An evaluation of event rates in both CHRONICLE and CONTROL patients for whom paired data were available from both the six-month randomized follow-up period and the subsequent six months revealed the following:
    - The average event rate among CHRONICLE patients remained low in both the 0-6 and 6-12 months time periods.
    - The event rate among CONTROL patients markedly decreased from 0.81 to 0.55 between the 0-6 and 6-12 months time periods, indicating that the initiation of IHM

Guided Care in the CONTROL group following completion of the randomized follow-up period resulted in an improvement similar to that of the CHRONICLE group.

These results support the continued successful implementation of IHM Guided Care beyond the requirements of the clinical protocol.

6. Summary

Until now, heart failure management in the ambulatory setting has been limited to clinical assessment during outpatient visits, and the approximation of volume status using symptoms and weight changes as reported by the patient from home. Access to ambulatory hemodynamic information provided by the Chronicle IHM allows clinicians to proactively monitor important clinical parameters remotely and potentially intervene earlier in the evolution of heart failure decompensation events.

The COMPASS-HF study did not meet its pre-specified primary effectiveness endpoint. Given: (1) the lower than hypothesized event rate in the CONTROL group (likely resulting from the high degree of interaction between clinicians and patients needed to maintain the single-blind design of the study), and (2) the high observed variability in events, the COMPASS-HF study was under-powered to detect the hypothesized effectiveness difference in a statistically significant manner.

A post-hoc analysis of a commonly reported endpoint in heart failure trials demonstrated a significant reduction in the relative risk of a heart failure-related hospitalization.

These results demonstrated the dynamic nature of intracardiac pressures, the association between hypervolemia and decompensated heart failure, and the utility of continuous ambulatory intracardiac pressure monitoring to decrease heart failure morbidity.

When considering: (1) the demonstrated accuracy, reliability, and safety of the IHM system; (2) the direction of the primary effectiveness endpoint; (3) the consistent pattern of rising filling pressures prior to a heart failure decompensation; (4) the assurance that frequent volume adjustment interventions are safe, and (5) the supporting results of the post-hoc analyses, on balance, the evidence generated over the last eight years support the favorable clinical impact of IHM Guided Care in reducing heart failure morbidity.

7. Proposed Indication for Use

The Chronicle 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.

8. Conditions of Approval Study

In the event of FDA approval, the sponsor is committed to continue the collection of clinical evidence in support of the application of this technology. The primary purpose of the proposed Conditions of Approval Study (as requested by the FDA) will be to test for equivalence in long-term mortality, comparing patients managed using the Chronicle IHM to a concurrent control group not receiving the device. This study also includes primary endpoints to evaluate system safety and the impact of IHM Guided Care on heart failure-related events over a two-year

follow-up period. Centers nominated for this Conditions of Approval study will be carefully selected for their ability to integrate this technology into their heart failure program. The study will enroll approximately 800 patients and will include centers new to IHM Guided Care (i.e. centers that did not participate in COMPASS-HF). A detailed study protocol has been submitted to the FDA as part of the Chronicle PMA, and the sponsor continues to work with the agency to finalize the study design.

9. Post Market Release Training & Education

The measurement of intracardiac and pulmonary artery pressures to assess volume status is generally familiar to physicians who manage heart failure; however, the use of longitudinal, trended pressure data in the ambulatory setting is novel. Therefore, the sponsor is committed to ensuring adequate training and education to clinicians who opt to integrate this technology into their practice. To that end, a comprehensive training plan has been developed for those clinicians who will be involved in either the implant of the Chronicle IHM or in caring for heart failure patients using data derived from the system.

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