GUIDE-HF

Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF)

NCT03387813

[redacted]

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Statistical Analysis Plan (SAP)

Sponsor: Abbott

[redacted]

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1.0 INTRODUCTION

This document is a statistical analysis plan for the CardioMEMS™ GUIDE-HF IDE trial, Clinical Investigation Plan (CIP) SJM-CIP-10170.

2.0 TRIAL OBJECTIVES

The Hemodynamic **GUIDE**d Management of **HF** (GUIDE-HF) IDE trial will include: a Randomized Arm and a Single Arm, with the following objectives:

GUIDE-HF Randomized Arm: The objective of the GUIDE-HF Randomized Arm is to determine if PA pressure-guided heart failure (HF) management using CardioMEMS™ improves health outcomes in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior heart failure hospitalization (HFH).

GUIDE-HF Single Arm: The objective of the GUIDE-HF Single Arm is to demonstrate equivalence of the effect of PA pressure-guided HF management using CardioMEMS™ on health outcomes between NYHA Class III patients with elevated NT-proBNP (or BNP) only and those with a prior HFH only.

3.0 TRIAL DESIGN

The GUIDE-HF IDE trial consists of two arms: a Randomized Arm and a Single Arm.

3.1.1 GUIDE-HF Randomized Arm

The GUIDE-HF Randomized Arm is a prospective, multi-center, randomized, controlled, single-blind clinical trial of the CardioMEMS™ HF System in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HFH. The trial will be conducted in 140 sites across North America. After signing the Informed Consent Form and confirmation of meeting all entry criteria for the Randomized Arm, subjects will complete baseline assessments. [redacted] subjects will receive a CardioMEMS™ HF System and, [redacted] be randomized in a 1:1 ratio into one of two groups:

- **Treatment Group:** Management of subjects based on PA pressure information derived from the CardioMEMS™ HF System
- **Control Group**: Management of subjects per standard of care (signs, symptoms, weight etc.) without knowledge of PA pressure information derived from the CardioMEMS™ HF System

Subjects will be considered enrolled in the Randomized Arm once all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted. However, subjects will only contribute towards the sample size and endpoint analysis following randomization. [redacted] No subject in the trial, regardless of treatment group, will have direct access to their uploaded PA pressure information. Investigators and clinical trial personnel will not have access to uploaded pressure information for subjects in the Control Group. Efforts will be made to ensure that subjects in the Treatment and Control Groups of the Randomized Arm will have communications with the sites at a similar

frequency, using only a pre-specified telephone script. Both Treatment and Control Group subjects will be contacted at least once every two weeks for the first three months post-implantation, and at least monthly from three months until the 12 month follow-up visit. [redacted]

The GUIDE-HF Randomized Arm will enroll approximately 1000 subjects (500 per group) at approximately 140 sites. Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months.

3.1.2 GUIDE-HF Single Arm

The GUIDE-HF Single Arm is a prospective, multi-center, single-arm clinical trial of the CardioMEMS™ HF System in North America in NYHA Class III HF patients, with either elevated NT-proBNP (or BNP) and/or a prior HFH. After signing the Informed Consent Form and confirmation of meeting all entry criteria for the Single Arm, subjects will complete baseline assessments. Within 30 days of consent, subjects will receive a CardioMEMS™ HF System. Subjects will be considered enrolled in the Single Arm once all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted. However, subjects will only contribute towards the endpoint analysis following successful implantation. Subjects will upload PA pressure information daily, and receive HF management guided by PA pressure information.

The GUIDE-HF Single Arm will enroll approximately 2600 subjects at approximately 140 sites. Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months.

4.0 TRIAL ENDPOINTS

4.1.1 GUIDE-HF Randomized Arm

The GUIDE-HF Randomized Arm will evaluate one primary endpoint, several secondary endpoints, and several descriptive endpoints. All endpoints will be compared between the Treatment and Control Groups, unless specified elsewhere.

4.1.1.1 GUIDE-HF Randomized Arm: Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (referred to as the Composite Endpoint). Emergency department visits and hospital outpatient observation visits involving intravenous diuretics, along with HFHs, are included in the primary endpoint, as the duration of hospitalization can vary, and decompensation events requiring intravenous diuretic therapy impact subject quality-of-life and mortality, regardless of form (inpatient or outpatient). The following events will be included in the composite: 1) hospitalization (≥ 24 hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy; 2) an unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit, or hospital inpatient visit, and intravenous administration of diuretic therapy; and 3) all-cause mortality. All events contributing to the primary endpoint will be adjudicated by an independent Clinical Events Committee (CEC). In rare instances, CEC discretion may be used to determine whether additional criteria would identify a decompensation event that could represent a valid contribution to the primary endpoint (e.g., ultra-filtration in lieu of diuretics).

4.1.1.2 GUIDE-HF Randomized Arm: Secondary Safety and Effectiveness Endpoints

The secondary effectiveness endpoints are:

- Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
- Health status at baseline, 6, and 12 months post-implantation as assessed by the EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire
- Health status at baseline, 6, and 12 months post-implantation as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12.
- Six Minute Hall Walk (6MHW) test at baseline, 6, and 12 months post-implantation
- In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
    - HFH at 12 months post-implantation
    - Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
    - All-cause mortality at 12 months

The secondary safety endpoint is Freedom from Device/System Related Complications (DSRC) over 12 months post-implantation.

4.1.1.3 GUIDE-HF Randomized Arm: Descriptive Endpoints

Descriptive endpoints are reported using only summary statistics and no hypothesis tests will be performed. Differences (or ratios) will be provided but no p-values will be generated. Also, the descriptive endpoints will not be used for making claims or changing the labelling. Please see Section 5.1.3 for additional details regarding the analysis of the descriptive endpoints. All mortality and hospitalization-related components of the primary endpoints will be adjudicated by the CEC. The following additional data will be collected and reported by Treatment and Control group:

- Cardiovascular mortality at 12 months post-implantation
- All-cause hospitalizations at 12 months post-implantation
- Frequency of subject PA pressure uploads through 12 months
- Frequency of clinician review of subject PA pressure uploads at 12 months
- HF medication changes at 12 months
- PAP measurements from baseline through 12 months
- NT-proBNP (or BNP) at baseline, 6, and 12 months
- HFHs at 12 months post-implantation compared to HFHs in the 12 months prior to implantation

4.1.2 **GUIDE-HF Single Arm**

The GUIDE-HF Single Arm will evaluate one primary endpoint, several secondary endpoints, and several descriptive endpoints. The GUIDE-HF Single Arm endpoints will be evaluated when all subjects have completed 12 month follow up or crossed the 12-month visit window.

4.1.2.1 GUIDE-HF Single Arm: Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (same as for the Randomized Arm), to be compared between subjects with an elevated NT-proBNP (or BNP) only and subjects with a prior HFH only. Subjects who have both elevated NT-proBNP (or BNP) and a prior HFH will not be included in the analysis for the primary endpoint. All events contributing to the primary endpoint will be adjudicated by the CEC. In rare instances, CEC discretion may be used to determine whether additional criteria would identify a decompensation event that could represent a valid contribution to the primary endpoint (e.g., ultra-filtration in lieu of diuretics).

4.1.2.2 GUIDE-HF Single Arm: Secondary Safety and Effectiveness Endpoints

The secondary effectiveness endpoints are:

- Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
- HFHs at 12 months post-implantation compared to HFHs in the 12 months prior to implantation
- In addition, the components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
    - HFH at 12 months post-implantation
    - Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
    - All-cause mortality at 12 months post-implantation.

The secondary safety endpoint is Freedom from DSRC over 12 months post-implantation.

4.1.2.3 GUIDE-HF Single Arm: Descriptive Endpoints

Descriptive endpoints are reported using only summary statistics and no hypothesis tests will be performed. Differences (or ratios) will be provided but no p-values will be generated. Also, the descriptive endpoints will not be used for making claims or changing the labelling. Please see Section 5.2.3 for additional details regarding the analysis of the descriptive endpoints. All mortality and hospitalization-related components of the primary endpoints will be adjudicated by the CEC. The following additional data will be collected and analyzed:

- Health status at baseline, 6, and 12 months post-implantation as assessed by EQ-5D-5L
- Health status at baseline, 6, and 12 months post-implantation as assessed by the KCCQ-12
- 6MHW test at baseline, 6, and 12 months post-implantation
- Cardiovascular mortality at 12 months post-implantation
- All-cause hospitalizations at 12 months post-implantation
- Frequency of subject PAP uploads through 12 months
- Frequency of clinician review of subject PAP uploads through 12 months
- HF medication changes through 12 months
- PAP measurements from baseline through 12 months
- NT-proBNP (or BNP) at baseline, 6 months, and 12 months

5.0 STATISTICAL METHODS

The following section describes the hypotheses and statistical methods for the clinical trial and justification of the design. Hypothesis tests will be 1-sided and conducted at a significance level of 2.5% unless stated otherwise.

5.1 GUIDE-HF Randomized Arm

5.1.1 GUIDE-HF Randomized Arm - Primary Endpoint

5.1.1.1 Hypothesis

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management, the following hypothesis will be tested:

H_0: Hazard ratio (HR) for the Composite Endpoint at 12 months (Treatment to Control) ≥ 1
H_1: HR for the Composite Endpoint at 12 months (Treatment to Control) < 1

In mathematical form, the hypotheses are defined as follows:

H_0: $e^{\beta 1} \geq 1$
H_1: $e^{\beta 1} < 1$

where e is the exponential function and β_1 is the regression coefficient obtained from the covariate representing randomized group (Treatment or Control) [redacted]

[redacted]

[redacted]

5.1.1.2 Analysis Methods

[redacted]

5.1.1.3 Sample Size

[redacted]

[redacted]

5.1.1.4 Analysis Population

The analysis population will include subjects randomized to either Treatment or Control group.

5.1.1.5 Poolability Analysis

[redacted]

[redacted]

5.1.1.6 Sensitivity Analysis

[redacted]

[redacted]

5.1.1.7 Subgroup Analysis

[redacted]

[redacted]

5.1.2 GUIDE-HF Randomized Arm: Secondary Safety and Effectiveness Endpoints

The secondary effectiveness endpoints of the GUIDE-HF Randomized Arm are the composite of HFH and emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation (i.e., HFH + HFH Equivalents) as well as health status, as assessed by the EQ-5D-5L Questionnaire and the KCCQ-12, and the 6MHW test at baseline, 6, and 12 months post-implantation. In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints: HFH at 12 months post-implantation, HFH Equivalents at 12 months post-implantation, and all-cause mortality at 12 months post-implantation. [redacted] The analysis population for the secondary effectiveness endpoints will include subjects randomized to either Treatment or Control groups.

[redacted]

The secondary safety endpoint of the GUIDE-HF Randomized Arm is freedom from DSRCs at 12 months post-implantation. The analysis population for the secondary safety endpoint will include subjects enrolled in the Randomized Arm (i.e. with an attempted implant, whether successful or unsuccessful).

5.1.2.1 HFH + HFH Equivalents at 12 months post-implantation

5.1.2.1.1 Hypothesis

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management with respect to HFH + HFH Equivalents, the following hypothesis will be tested:

H_0: HR for HFH + HFH Equivalents at 12 months (Treatment to Control) ≥ 1
H_1: HR for HFH + HFH Equivalents at 12 months (Treatment to Control) < 1

[redacted]

5.1.2.1.2 Analysis Methods

[redacted]

5.1.2.1.3 Sample Size

[redacted]

5.1.2.1.4 Missing Data Sensitivity Analyses

[redacted]

[redacted]

5.1.2.2 EQ-5D-5L at 6 and 12 Months

5.1.2.2.1 Hypothesis

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management with respect to the EQ-5D-5L, the following hypothesis will be tested for the EQ-5D-5L visual analogue scale (VAS):

H_0: Treatment effect$_{\text{EQ-5D-5L VAS}} \leq 0$
H_1: Treatment effect$_{\text{EQ-5D-5L VAS}} > 0$

[redacted]

5.1.2.2.2 Analysis Methods

[redacted] The null hypothesis will be rejected if the [redacted] shows benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

5.1.2.2.3 Missing Data

[redacted]

5.1.2.2.4 Sensitivity Analysis

[redacted]

[redacted]

5.1.2.3 KCCQ-12 at 6 and 12 Months

5.1.2.3.1 Hypothesis

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management with respect to the KCCQ-12, the following hypothesis will be tested for the KCCQ-12:

H_0: Treatment effect$_{\text{KCCQ-12 Overall Summary Score}} \leq 0$
H_1: Treatment effect$_{\text{KCCQ-12 Overall Summary Score}} > 0$

[redacted]

5.1.2.3.2 Analysis Methods

[redacted] The null hypothesis will be rejected if the [redacted] show benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

[redacted]

5.1.2.3.3 Missing Data

[redacted]

5.1.2.3.4 Sensitivity Analysis

[redacted]

5.1.2.4 6MHW test at 6 and 12 Months

5.1.2.4.1 Hypothesis

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management with respect to the 6MHW test, the following hypothesis will be tested for the 6MHW test:

H_0: Treatment effect$_{6MHW} \leq 0$
H_1: Treatment effect$_{6MHW} > 0$

[redacted]

5.1.2.4.2 Analysis Methods

[redacted]

[redacted] The null hypothesis will be rejected if the [redacted] show benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

5.1.2.4.3 Missing Data

[redacted]

5.1.2.4.4 Sensitivity Analysis

[redacted]

5.1.2.5 Individual Components of the Primary Endpoint

The individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:

5.1.2.5.1 HFH at 12 months post-implantation

[redacted]

5.1.2.5.2 HFH Equivalents at 12 months post-implantation

[redacted]

5.1.2.5.3 All-Cause Mortality at 12 months post-Implantation

[redacted]

[redacted]

5.1.2.6 Secondary Safety Endpoint: Freedom from DSRCs over 12 Months Post-Implantation

The secondary safety endpoint of freedom from DSRCs is defined as an adverse event that is related or possibly related to the system (wireless pressure sensor or external electronics) and has at least one of the following characteristics:

- is treated with invasive means (other than intramuscular medication or a right heart catheterization which is used for diagnostic purposes)
- results in the death of the subject
- results in the explant of the device

The frequency of DSRCs and the frequency and proportion of subjects having freedom from DSRCs at 12 months post-implantation will be reported by group.

5.1.3 **GUIDE-HF Randomized Arm: Descriptive Endpoints**

Each of the following descriptive endpoints will be evaluated for the Treatment and Control groups separately and will be descriptively compared: [redacted] The analysis population will include subjects randomized into the Treatment and Control groups.

5.1.3.1 Cardiovascular Mortality at 12 Months Post-Implantation

[redacted]

5.1.3.2 All-Cause Hospitalizations at 12 Months Post-Implantation

[redacted]

5.1.3.3 Frequency of Subject PA Pressure Uploads through 12 Months

[redacted]

5.1.3.4 Frequency of Clinician Review of Subject PAP Uploads through 12 Months

[redacted]

[redacted]

5.1.3.5 HF Medication Changes through 12 Months

[redacted]

5.1.3.6 PAP Pressure Measurements from Baseline through 12 Months

[redacted]

5.1.3.7 NT-proBNP and BNP at Baseline, 6 Months, and 12 Months

[redacted]

5.1.3.8 HFHs at 12 months post-implantation compared to HFHs 12 months prior to implantation

[redacted]

5.2 GUIDE-HF Single Arm

5.2.1 GUIDE-HF Single Arm - Primary Endpoint

5.2.1.1 Hypothesis

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (same as for the Randomized Arm), to be compared between subjects with an elevated NT-proBNP (or BNP) only and subjects with a prior HFH only. To demonstrate equivalence of outcomes between elevated NT-proBNP (or BNP) only subjects and prior HFH only subjects, the following hypothesis will be tested for the Composite Endpoint at 12 months:

H_{0a}: ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] ≤ -0.2877
H_{0b}: ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] ≥ 0.2877
H_1: -0.2877 < ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] < 0.2877
Where ln is the natural log

[redacted]

5.2.1.2 Analysis Methods

The hypothesis will be tested at the 5% significance level. [redacted]

[redacted]

[redacted]

[redacted]

Propensity Stratification Method

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

5.2.1.3 Sample Size

[redacted]

[redacted]

5.2.1.4 Analysis Population

The analysis population will include enrolled subjects having a successful implant with elevated NT-proBNP (or BNP) level only and subjects with a prior HFH only. Subjects with both elevated NT-proBNP (or BNP) and prior HFH will not be included in the analysis for the primary endpoint.

5.2.1.5 Poolability Analysis

[redacted]

5.2.1.6 Sensitivity Analysis

[redacted]

[redacted]

[redacted]

5.2.1.7 Subgroup Analysis

[redacted]

[redacted]

5.2.2 **GUIDE-HF Single Arm: Secondary Safety and Effectiveness Endpoints**

The secondary effectiveness endpoints of the GUIDE-HF Single Arm are HFH + HFH Equivalents and the comparison of annualized rate of recurrent HFH at 12 months post-implantation to the annualized rate of recurrent HFH in the 12 months prior to implantation. In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints: HFH at 12 months post-implantation, emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation, and all-cause mortality at 12 months post-implantation. [redacted] The analysis population for the secondary effectiveness endpoints will include subjects enrolled into the Single Arm and successfully implanted regardless of NT-proBNP (or BNP) and HFH history unless otherwise noted.

The secondary safety endpoint of the GUIDE-HF Single Arm is freedom from DSRCs at 12 months post-implantation. The analysis population for the secondary safety endpoint will include subjects enrolled in the Single Arm (i.e. with an attempted implant, whether successful or unsuccessful).

[redacted]

5.2.2.1 HFH + HFH Equivalents at 12 months post-implantation

5.2.2.1.1 Hypothesis

To demonstrate equivalence of HFH + HFH Equivalents between elevated NT-proBNP (or BNP) only subjects and prior HFH only subjects, the following hypothesis will be tested for HFH + HFH Equivalents at 12 months:

H_{0a}: ln[HR for HFH + HFH Equivalents (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] ≤ -0.2877
H_{0b}: ln[HR for HFH + HFH Equivalents (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] ≥ 0.2877
H_1: -0.2877 < ln[HR for HFH + HFH Equivalents (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] < 0.2877
Where ln is the natural log

[redacted]

5.2.2.1.2 Analysis Methods

[redacted]

5.2.2.1.3 Missing Data Sensitivity Analyses

[redacted]

5.2.2.1.4 Sample Size

[redacted]

5.2.2.2 HFHs at 12 months post-implantation compared to HFHs 12 months prior to implantation

5.2.2.2.1 Hypothesis

The secondary endpoint will be evaluated using the following hypothesis:

H_0: HR for annualized HFH at 12 months (Rate at 1 year post-implant to Rate at 1 year pre-implant) ≥ 1
H_1: HR for annualized HFH at 12 months (Rate at 1 year post-implant to Rate at 1 year pre-implant) < 1

[redacted]

5.2.2.2.2 Analysis Population

This secondary endpoint will be evaluated for the cohort of subjects enrolled into the Single Arm following successful implantation regardless of NT-proBNP (or BNP) and HFH history.

5.2.2.2.3 Analysis Methods

[redacted] The null hypothesis will be rejected if the upper limit of the 1-sided, 97.5% CI for the HR of Post-Implant to Pre-Implant is less than 1.

5.2.2.2.4 Sample Size

[redacted]

5.2.2.2.5 Subgroup Analysis

The following 3 subgroups will be used for descriptive analyses (rates, hazard ratio and 2-sided 95% CI for the HR) of this secondary endpoint:

a) elevated NT-proBNP only
b) prior HFH only and
c) both elevated BNP and HFH.

[redacted]

5.2.2.3 Individual Components of the Primary Endpoint

5.2.2.3.1 HFH at 12 months post-implantation

[redacted]

5.2.2.3.2 HFH Equivalents at 12 months post-implantation

[redacted]

5.2.2.3.3 All-Cause Mortality at 12 months post-Implantation

[redacted]

5.2.2.4 Secondary Safety Endpoint: Freedom from DSRC over 12 Months Post-Implantation

The secondary safety endpoint of freedom from DSRC is defined as an adverse event that is related or possibly related to the system (wireless pressure sensor or external electronics) and has at least one of the following characteristics:

- is treated with invasive means (other than intramuscular medication or a right heart catheterization which is used for diagnostic purposes)
- results in the death of the subject
- results in the explant of the device

The frequency of DSRCs and the frequency and proportion of subjects having freedom from DSRCs at 12 months post- implantation will be reported for the overall cohort as well as for each pre-defined subject group.

5.2.3 **GUIDE-HF Single Arm: Descriptive Endpoints**

Each of the following descriptive endpoints will be evaluated for the full cohort, as well as for each of the three pre-defined subject groups separately: a) elevated NT-proBNP (or BNP) only subjects, b) prior HFH only subjects, and c) both elevated NT-proBNP (or BNP) and a prior HFH subjects. These descriptive endpoints will be reported using these descriptive statistics: n, mean, median, standard deviation, minimum and maximum for continuous variables; frequency and percent for categorical variables; annualized rates for time-to-event variables (or time-between-events variables for recurrent-data endpoints).

5.2.3.1 EQ-5D-5L at 6 and 12 months

[redacted]

[redacted]

5.2.3.2 KCCQ-12 at 6 and 12 months

[redacted]

5.2.3.3 6MHW test at 6 and 12 months

[redacted]

5.2.3.4 Cardiovascular Mortality at 12 Months Post-Implantation

[redacted]

5.2.3.5 All-Cause Hospitalizations at 12 Months Post-Implantation

[redacted]

5.2.3.6 Frequency of Subject PA Pressure Uploads through 12 Months

[redacted]

[redacted]

5.2.3.7 Frequency of Clinician Review of Uploads through 12 Months

[redacted]

5.2.3.8 HF Medication Changes through 12 Months

[redacted]

5.2.3.9 PAP Pressure Measurements from Baseline over 12 Months

[redacted]

5.2.3.10 BNP and NT-proBNP at Baseline, 6 Months and 12 Months

[redacted]

5.3 Sensitivity Analyses to Evaluate Possible Impact of COVID-19 for Randomized Arm

5.3.1 Primary Endpoint

[redacted]

5.3.2 Secondary Effectiveness Endpoints

5.3.2.1 HFH + HFH Equivalents at 12 months post-implantation

[redacted]

5.3.2.2 EQ-5D-5L at 6 and 12 Months

[redacted]

5.3.2.3 KCCQ-12 at 6 and 12 Months

[redacted]

5.3.2.4 6MHW test at 6 and 12 Months

[redacted]

5.3.3 **Descriptive Secondary Effectiveness Endpoints (Individual Components of the Primary Endpoint):**

5.3.3.1 HFH at 12 months post-implantation

[redacted]

5.3.3.2 HFH Equivalents at 12 months post-implantation

[redacted]

5.3.3.3 All-Cause Mortality at 12 months post-Implantation

[redacted]

[redacted]

5.4 Sensitivity Analyses to Evaluate Possible Impact of COVID-19 Single Arm

5.4.1 Primary Endpoint

[redacted]

5.4.2 Secondary Effectiveness Endpoints

5.4.2.1 HFH + HFH Equivalents at 12 months post-implantation

[redacted]

5.4.2.2 HFHs at 12 months post-implantation compared to HFHs 12 months prior to implantation

[redacted]

5.4.3 Descriptive Secondary Effectiveness Endpoints, Individual Components of the Primary Endpoint:

5.4.3.1 HFH at 12 months post-implantation

[redacted]

[redacted]

5.4.3.2 HFH Equivalents at 12 months post-implantation

[redacted]

5.4.3.3 All-Cause Mortality at 12 months post-Implantation

[redacted]

5.4.4 Descriptive Endpoints

5.4.4.1 EQ-5D-5L at 6 and 12 Months

[redacted]

5.4.4.2 KCCQ-12 at 6 and 12 Months

[redacted]

5.4.4.3 6MHW test at 6 and 12 Months

[redacted]

[redacted]

5.5 Overall Sample Size

The sample size required for evaluation of the Randomized Arm and Single Arm primary endpoints is approximately 3600 (1000 for the Randomized Arm and 2600 for the Single Arm). [redacted]

[redacted]

5.6 Timing of Analysis

[redacted]

5.7 Trial Success

Each arm of the Guide-HF trial (Randomized Arm and Single Arm) will be evaluated separately and have separate criteria for success. The Randomized Arm will be considered successful if its primary endpoint is met. Likewise, the Single Arm will be considered successful only if its primary endpoint is met. [redacted]

5.8 Statistical Criteria for Termination

There are no statistical criteria for termination of this trial.

5.9 Justification of Clinical Trial Design

The Randomized Arm will evaluate the effectiveness of HF management using the CardioMEMS™ HF System by comparing outcomes against HF management on the basis of standard of care alone. The Randomized Arm is a prospective, randomized, controlled, single-blind investigation, providing the highest level of evidence [13, 14] to expand the indication for the CardioMEMS™ HF system to patients with elevated NT-proBNP (or BNP) or NYHA Class II or Class IV. [redacted]

The Single Arm is a prospective, multi-center, clinical trial of the CardioMEMS™ HF System in NYHA Class III HF patients with either elevated NT-proBNP (or BNP) levels and/or a prior HFH. It will be used to demonstrate equivalence of clinical outcomes between NYHA Class III subjects with an elevated NT-proBNP (or BNP) only and those with a prior HFH only. Results of this clinical trial will be used to support an expanded indication to subjects with elevated NT-proBNP (or BNP) for NYHA Class III patients.

The primary endpoint of both the Randomized Arm and Single Arm, the composite of HF events and mortality, is a clinically relevant endpoint for HF patients, and has been used in previous IDE trials [15,16] and was recommended for use in future clinical trials by consensus among HF experts [17].

[redacted]

The secondary endpoints of the Randomized Arm (not including the individual components of the primary endpoint) were selected for the following reasons:

- Change in EQ5D-5L – Use of EQ5D in cardiovascular studies has increased in recent years and published studies provide evidence of its validity and reliability [18]. The EQ5D-5L was shown to have better measurement properties than the original EQ5D [19].
- Change in KCCQ-12 – This instrument has been shown to be a valid, reliable, responsive, and prognostically important measure of health status for HF patients [20].
- Improvement in 6MHW test – In congestive HF patients, the 6MHW test provides an objective assessment of exercise capacity that supplements clinical information obtained from medical history and physical examination [21].

The secondary endpoint of the Single Arm (not including the components of the primary endpoint), the comparison of HFH in the 12 months prior compared to the 12 months post-implantation, was selected as it provides an objective measure of whether individual hospitalizations have decreased compared to pre-implantation and has been used in prior retrospective analyses in similar patient populations [22].

The secondary safety endpoint used for both the Randomized Arm and Single Arm was selected as it has been used in previous IDE and post-approval trials for implantable hemodynamic monitoring devices, including the CardioMEMS™ HF System.

5.10 Adjustment for Multiple Testing

[redacted]

[redacted]

5.11 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical trial report or statistical report containing the analysis results.

6.0 DEMOGRAPHICS AND ADDITIONAL DATA

Baseline and demographic variables, and additional data will be reported for the Randomized Arm and the Single Arm.

6.1 Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized: [redacted]

The following baseline and demographic variables will be summarized: gender, age, ethnicity, race, NYHA class, height, weight, BMI, blood pressure, heart rate, ejection fraction and other vital signs.

Medical and surgical history (including cardiovascular history and CRT device history along with major comorbidities), physical examination, heart failure assessment, and cardiac history will be summarized.

6.2 Adverse Events

Adverse device effects (ADE), serious adverse device effects (SADE), unanticipated adverse device effects (UADE), serious adverse events (SAE) (cardiovascular in nature) will be summarized for subjects enrolled in this trial as number of events, the number and percentage of subjects with events and event rate as number of events/subject-month.

6.3 Withdrawal

Subject withdrawals will be summarized by reason for withdrawal for subjects who have withdrawn from the trial prior to 12 months.

6.4 Protocol Deviation

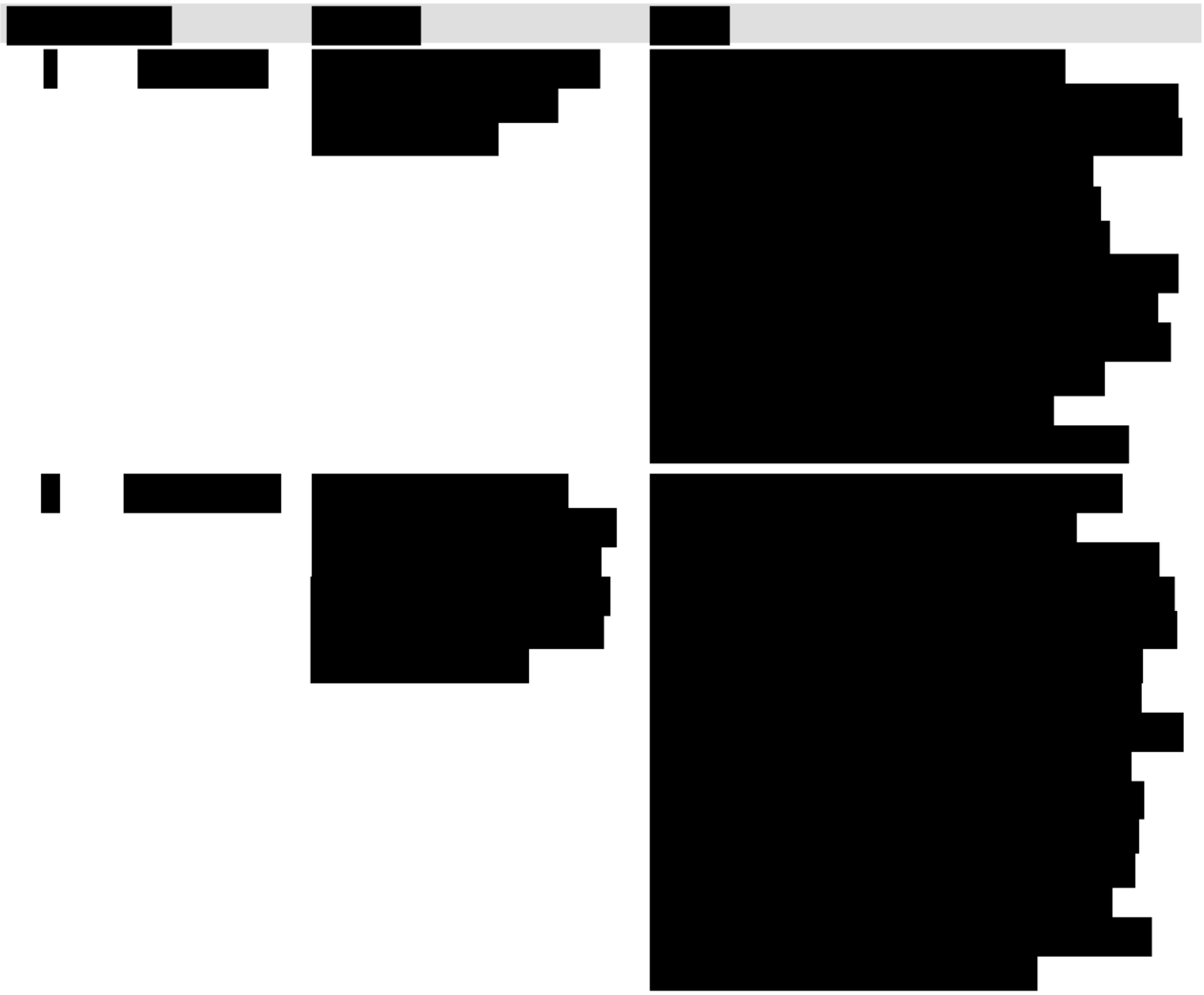
Protocol deviations will be summarized for subjects in whom a protocol deviation was reported.

7.0 REVISION DESCRIPTION

[redacted]

Table 1: Revision History

[redacted]



APPENDIX A: POWER AND SAMPLE SIZE CALCULATIONS

[redacted]

[redacted]

[redacted]

}

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX B: MISSING DATA HANDLING IN KCCQ SCORING ALGORITHMS

[redacted]

APPENDIX D: REFERENCES

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[redacted]