Cardiac Rhythm Management Division

STATISTICAL ANALYSIS PLAN
FOR THE

ST MONITORING TO DETECT ACS EVENTS IN ICD PATIENTS STUDY

(Analyze ST)

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1.0 INTRODUCTION

This document contains the statistical analysis plan for the Analyze ST IDE study using St. Jude Medical ICD systems. The Analyze ST study will include the following device models:

- Fortify® ST family of devices
- Fortify Assura® St family of devices
- Ellipse® family of devices

These devices will be collectively referred to as the Investigational Devices except where otherwise specified. All analyses will be carried out on the study endpoints as well as on additional data specified in this document.

2.0 PURPOSE

The intent of this study is to demonstrate the safety and effectiveness of the diagnostic ST Monitoring Feature in the Investigational Devices. Effectiveness of the device will be evaluated by analyzing the sensitivity of the ST Monitoring Feature to detect clinical events. In addition, safety of the ST Monitoring Feature will be evaluated by demonstrating a low percentage of patients with false positive events.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design and Patient Follow-up

This is a prospective, non-randomized, multicenter, pivotal IDE study evaluating the Investigational Devices with the ST Monitoring Feature. The Analyze ST study is designed to demonstrate the safety and efficacy of the ST Monitoring Feature in the Investigational Devices. The sensitivity of the ST Monitoring Feature for detecting acute coronary syndrome events will be the primary efficacy endpoint. The primary safety endpoint will be assessed by reporting the percentage of patients who experience a false positive detection during the 12 months following a 3 month run-in period.

The goal of the 3 month run-in period is to:

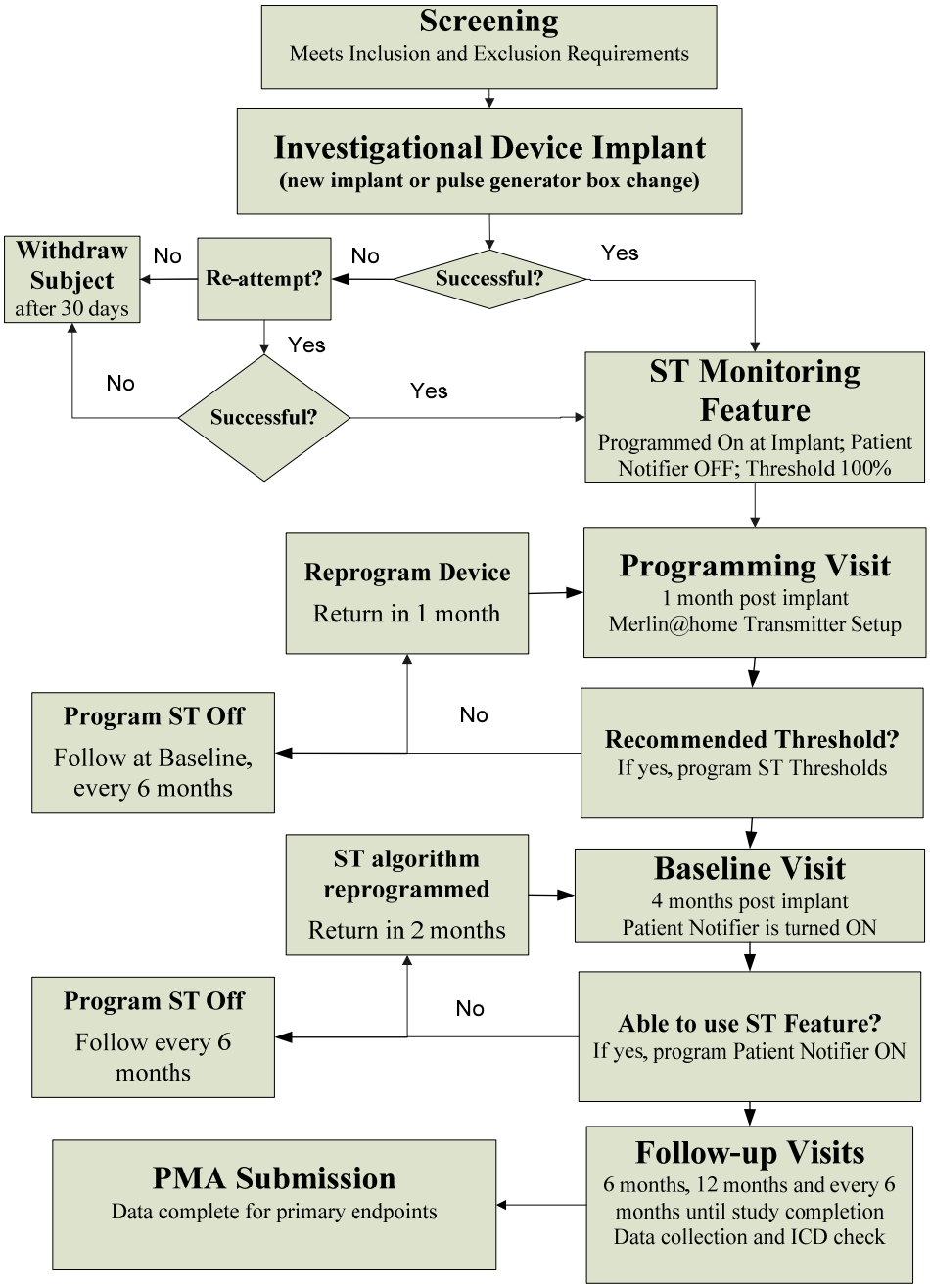
1. Identify patients whose EGM rhythm or morphology is unsuitable for chronic ST monitoring
2. Provide data collection for review in order to adjust or optimize ST feature parameters

Data collection for the purposes of the FDA market approval application will be considered to be complete when the primary safety endpoint data are available and at least 41 clinical events have occurred. It is estimated that up to 5,228 patients at

approximately 200 centers will be enrolled in the study with a follow up of 12 months to meet the primary study endpoints.

A flow diagram of the study design is below.

Study Flow Diagram



3.2 Clinical Event Description and CEC Adjudication

Three types of events are defined in the sections below. All clinical events will be adjudicated by a Clinical Events Committee (CEC) consisting of a blinded panel of independent experts. Once the CEC adjudicates the Clinical Events, and per defined criteria in section 3.2.2, all Type I ST episodes will be classified as either False Positive or True Positive events. In addition, any Clinical Event that was not associated with a Type I ST episode detection will be classified as either False Negative or True Negative.

3.2.1 Clinical Event Committee

The CEC will include at a minimum, 2 interventional cardiologists and 2 electrophysiologists. Physicians on the CEC will not participate in the study as investigators and when reviewing events will be blinded to any patient or site information. The purpose of the CEC is to adjudicate all clinical events. Specifically:

- Classify clinical events as either an Acute Coronary Syndrome (ACS) Event, a Precursor Event, or a Non Event. Non Events will be further classified as either a Transient Ischemic Event or a Non Ischemic Event. Review all deaths, and adverse events associated with diagnostic testing or procedures performed as a result of a Type I ST Episode Detection and determine relationship to system and/or procedure.
- Review all baseline surface ECGs to determine the presence or absence of any conduction abnormality.
- Review all complications and all cardiovascular related adverse events

3.2.2 Clinical Events

ACS Events

An ACS event is defined as any of the following:

- Death due to a myocardial infarction
- A new Q-wave myocardial infarction on 12-lead ECG
- ST elevation myocardial infarction
- Biomarker evidence of acute myocardial damage*
- Evidence of new plaque rupture by invasive testing (i.e., IVUS) as adjudicated by the blinded Clinical Events Committee
- The presence of TIMI myocardial perfusion grade 0 or 1 consistent with acute injury of the myocardium from embolization
- New surface ECG ST depression or elevation treated with thrombolytic medication

- New surface ECG ST depression or elevation with new or progressive flow-limiting ischemia proven by non-invasive or invasive testing.
- Angiographic stenosis ≥70% adjudicated by the blinded Clinical Events Committee as flow-limiting.
- An event that leads to a clinically warranted percutaneous coronary intervention (PCI) or revascularization as determined by the blinded Clinical Events Committee. Clinically warranted is defined as:
    - Angiographically visualized stenosis ≥70% correlating with the vascular distribution in which a 12-lead surface ECG documents changes consistent with ischemia or injury in 2 or more contiguous leads
    - Angiographically visualized stenosis ≥70% correlating with a vascular distribution shown to have ongoing ischemia by non-invasive stress testing
    - New or progressive angiographically visualized stenosis ≥70% correlated with new or progressive anginal symptoms

*NOTE: It is recommended that the "Universal Definition of Myocardial Infarction" proposed by the Joint ESC/ACCF/AHA/WHF in 2007 be used to determine myocardial damage.

Precursor Events

A precursor event is defined as clinical symptoms of an impending ACS event followed by an ACS event within 10 days. Precursor events alone do not meet the ACS event criteria. Multiple precursor events may precede a single ACS. All precursor events will be adjudicated by the Clinical Event Committee (CEC). Symptoms identified as precursors will be grouped with the subsequent ACS event and counted as a single event. Individual precursor events will not be included in the statistical endpoint analysis.

Non Events

Non Events are defined as any clinical event that does not meet the criteria of an ACS Event or a Precursor Event. These events will be adjudicated by the CEC and will be further classified as either Transient Ischemic Events or as Non Ischemic Events.

3.2.3 Classification of Events

True Positive (TP): A Type I ST episode detection that occurs up to 72 hours prior to an ACS Event.

False Positive (FP): A Type I ST episode detection that occurs more than 72 hours prior to an ACS Event or that occurs in the absence of a true ACS Event.

True Negative (TN): Absence of a Type I ST episode detection during a Non Event.

False Negative (FN): Absence of a Type I ST episode detection within 72 hours prior to an ACS Event.

3.3 Patient Selection

3.3.1 Inclusion Criteria

Eligible patients will meet **all** of the following:

1. Have an indication for an ICD implantation or pulse generator change
2. Have documented coronary artery disease. Documented coronary artery disease is defined as having at least one of the following present a) evidence of a prior MI on ECG and/or cardiac enzymes, b) prior revascularization (by coronary artery bypass grafting or percutaneous coronary intervention) c) angina and/or ST-T wave abnormalities indicative of ischemia on exercise stress test, nuclear stress test, or echo stress test, or d) coronary artery disease diagnosed by coronary angiography.
3. Willing and able to comply with protocol requirements, including keeping all required visits
4. Willing to participate in the study and able to sign an IRB approved informed consent form
5. Willing and capable of using Merlin@home.
6. Be at least 18 years of age when enrolled in the study

3.3.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Are pacemaker dependent (defined as a need for ventricular pacing ≥ 20% of the time)
2. Have NYHA Class IV Heart Failure
3. Have persistent or permanent atrial fibrillation
4. Have a known history of intermittent Bundle Branch Block
5. Pregnant or planning a pregnancy during the study participation
6. Have a life expectancy of < 1 year due to any condition
7. Are currently participating in a clinical investigation that includes an active treatment arm

3.4 Device Description

The SJM ICD system is intended to provide ventricular anti-tachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. AF Suppression™ pacing is indicated for suppression of paroxysmal or persistent atrial fibrillation in patients with the above ICD indication and sinus node dysfunction. In addition, the Investigational Devices have an ST Monitoring Feature that has the ability to detect ST shifts, and to record and store the associated high fidelity IEGMs during those shifts. Refer to the User's Manual for more details.

The pulse generator, along with compatible leads, constitutes the implantable portion of the ICD system.

3.5 Evaluation of Safety

3.5.1 Preliminary Safety Assessment Phase

An initial assessment of the proportion of patients free from complications due to unnecessary procedures resulting from false positive events will be conducted on the first 500 patients to complete 6 months of follow-up.

3.5.2 Primary Endpoint

The primary safety endpoint will evaluate the percentage of patients experiencing false positive events with the use of the ST Monitoring Feature.

3.5.3 Secondary Endpoint

The secondary safety endpoint will evaluate the False Positive Rate (FPR) of the ST Monitoring Feature.

3.6 Evaluation of Efficacy

3.6.1 Primary Endpoint

The primary efficacy endpoint will evaluate the sensitivity of the ST Monitoring Feature to detect clinical events.

4.0 STATISTICAL METHODS

4.1 Randomization and Blinding

This is a prospective, non-randomized, multicenter, pivotal IDE study evaluating the Investigational Devices with the ST Monitoring Feature.

4.2 Data Safety and Monitoring Board

In order to ensure patient safety throughout the study, an independent DSMB will oversee the course of the study. The DSMB will periodically review safety data (percentage of patients with false positive events, False Positive Rate, and study-related adverse events), false negative events, and any procedures/hospitalizations resulting from false positives, even if they do not result in complications. The DSMB will provide a recommendation regarding continuation of the study to the Chairman of the Steering Committee for the study, who will in turn inform the sponsor. A copy of any written communication from the DSMB to the Sponsor regarding recommended changes to the study status, procedures or to the Informed Consent Form will be provided to the FDA during the annual report. If the DSMB recommends substantive changes to the protocol, these communications will be provided along with the applicable IDE supplement. The DSMB will also be informed of the Preliminary Safety Assessment and will be provided with the results when the report is submitted to the FDA. The DSMB will consist of at a minimum 2 cardiologists, 1 electrophysiologist, and 1 statistician. In order to prevent bias, the DSMB committee members will not participate in the study as investigators.

4.3 Analysis of Safety

4.3.1 Preliminary Safety Assessment Phase

An initial assessment of the proportion of patients free from complications due to unnecessary procedures resulting from false positive events will be conducted on the first 500 patients to complete 6 months of follow-up. In patients with an upgraded Fortify® ST device, the 6 months of follow-up begins with either their Baseline visit or the Baseline Upgrade visit (during which the firmware upgrade occurs). In patients with Fortify Assura ST® and Ellipse ST®, the 6 months of follow-up begins with the Baseline visit. For those patients with Fortify Assura ST® and Ellipse ST®, the survival time for patients who experience a complication will be calculated as the number of days from the Baseline visit (when the Patient Notifier is activated) to the date of the procedure-related complication. For those patients with Fortify® ST devices, the survival time will be calculated as the number of days from either the Baseline visit or the Baseline Upgrade visit (i.e., whichever visit the patient received the firmware upgrade) to the date of the procedure-related complication is first discovered. For patients who withdraw without experiencing a complication prior to analysis, their survival time will be censored at the date of withdrawal. For patients who have not experienced complications at the time of analysis, their survival time will be censored on the date of the analysis.

All patients who have the Patient Notifier turned ON at the Baseline visit or the Baseline Upgrade visit and have completed their 6-month follow up visit or 6 months of follow up since being upgraded will be included in this analysis.

Complications related to unnecessary procedures resulting from false positive events are defined as any procedure-related or test-related complications that occur in a patient in which a Type I ST episode is classified as a false positive according to the criteria described in section 3.2.3. All clinical events will be adjudicated by an independent and blinded Clinical Event Committee for the purposes of determining whether the event was related to ischemia or acute coronary syndrome and whether it was procedure or test related Complications related to procedures or tests may include, but are not limited to:

- Air embolism
- Allergic reaction to contrast media
- AV fistula
- Bleeding
- Cardiac tamponade
- Contrast nephropathy
- Formation of hematomas or cysts
- Infection
- Myocardial infarction
- Peripheral nerve injury
- Pneumothorax
- Pseudo-aneurysm
- Stent thrombosis
- Stroke
- Thromboemboli
- Venous occlusion
- Venous or cardiac perforation

Analysis

- A Kaplan-Meier estimate of the proportion of patients free from complications arising from a false positive event through the 6 month follow-up visit will be provided with a 95% lower bound on the estimate using Greenwood's formula for the variance of the Kaplan-Meier estimator. If no events have been observed, then a Clopper-Pearson 95% exact lower confidence bound for the proportion of patients free from complications due to unnecessary procedures resulting from false positive events will be provided.
- A tabular presentation of ER visits, doctor office visits, or any medical care will be presented, stratified by false positive, true positive and false negative events.
- The proportion of patients with false positive events, with the count of false positive, true positive and false negative events will be provided. A preliminary estimate of sensitivity will be calculated.
- The proportion of patients with the ST monitoring feature turned off after the Programming and Baseline visits will be tabulated along with the reason for the turning off the ST monitoring feature.
- Baseline demographics and site enrollment will be tabulated.

The above analyses will be presented overall and by the following subgroups:

- Coronary artery disease patients with cardiomyopathy
- Coronary artery disease patients without cardiomyopathy
- Patients with abnormal baseline ECGs, for each of six abnormal subgroup categories
- Patients with normal baseline ECGs
- Patients with arrhythmias
- Gender
- Patients alerted via Merlin.net and patients alerted via device Patient Notifier

Additional Analysis

An analysis will be performed that includes all clinical events using a GEE logit-link linear model to estimate the sensitivity with a working correlation that provides a robust estimator of the variance adjusting for multiple clinical events within patients.

An empirical analysis will be provided for the sensitivity of the ST Monitoring Feature to detect clinical events using the estimator described in the Primary Analysis section. The standard error of this empirical estimate will calculated as the standard deviation of a bootstrap distribution. The bootstrap distribution will be constructed using 1,000 bootstrap resamples. Each bootstrap resample will be performed at the patient level (in order to preserve the correlation structure of multiple events within one patient, if the occurs), and each resample will have a total sample size equal to the total number of evaluable patients. A two-sided 95% bootstrap confidence interval will be provided.

4.3.2 Primary Safety Endpoint

The ST Monitoring Feature will be evaluated by the percentage of patients with false positive events. The percentage of patients with false positive events is calculated as the number of patients who experience false positives divided by the number of evaluable patients. A False Positive occurs when a clinical event does not occur within 72 hours following a Type I ST episode.

The hypothesis is formally expressed as follows:

H_0: Percent of patients experiencing a false positive event in 12 months $\geq 15\%$
H_a: Percent of patients experiencing a false positive event in 12 months $< 15\%$

The desired outcome is to reject the null hypothesis at the 2.5% significance level. The null hypothesis will be rejected at the 2.5% significance level if the

upper bound of the 95% confidence interval for the percent of patients experiencing false positive events is less than 15%. The upper confidence bound will be calculated using the Wilson score interval method.

Patient Group

All enrolled patients who have a successful implant or system revision, complete the baseline follow up visit and have the ST Monitoring Feature and Patient Notifier turned ON will be included in the evaluation of this study endpoint. Data collection towards the study endpoint will begin after the Baseline visit.

Further, the analysis population for the primary safety endpoint will be those subjects with the Fortify® ST (upgraded), Fortify Assura® ST and Ellipse® ST. Data from subjects with a Fortify® ST device prior to being upgraded will not be included in this analysis.

Analysis

Primary Analysis

The primary analysis will be a complete case analysis where patients who are lost to follow-up before completing their 12 month visit without experiencing a false positive event will be considered non-evaluable and omitted from the analysis of the endpoint. Patients experiencing a false positive event and withdrawing before the 12 month visit will be included in the analysis. The proportion of patients experiencing false positives will be estimated by the number of patients experiencing a false positive event divided by the number of evaluable patients.

Imputation Analysis

A comparison of baseline characteristics of the subjects with missing data and those without missing data will be done to determine if there is evidence that the data are not missing at random (it is not possible to determine that data are missing at random). If the missing at random assumption is clearly violated by these comparisons, it is usually possible to find a sub-group that are not missing at random who have to be imputed differently, such as assigning the worst score to patients in the sub-group. If this resolves the missing at random difficulty, the sub groups will be given special scores and the remaining patients will be imputed as described above.

This analysis will use the patients from the complete case analysis to perform a logistic regression and an imputation procedure to impute false positive status for patients who were non-evaluable in the complete-case analysis. The imputations are described as follows: A logistic regression will be performed using the complete case patients, with the dependent variable dichotomous

false positive status and the independent variables for ischemic Cardiomyopathy and each of the four categories of non-ischemic Cardiomyopathies (Dilated, Hypertrophic, Restrictive and ARVD), age, gender, QRS duration > 120ms and EF% at the time of enrollment. The estimates of the coefficients and standard errors of the logistic regression will be used as the parameters of a multivariate normal distribution that will define the population of the logistic regression model parameters. Up to ten random samples logistic model parameters will be selected. For each random set of parameters, the non-evaluable patients will have their false positive status imputed as having experienced a false positive if their predicted logistic model response is >0.5, and not having experienced a false positive event otherwise. These imputed datasets will be created using PROC MI in SAS V9.2 or greater. An analysis of the hypothesis will be carried out for each complete imputed dataset, and the results will be combined across datasets to obtain one overall conclusion using PROC MIANALYZE in SAS V9.2 or greater.

Additional Analysis

An empirical analysis will be provided for the proportion of patients experiencing false positive events using the estimator described in the Primary Analysis section. The standard error of this empirical estimate will calculated as the standard deviation of a bootstrap distribution. The bootstrap distribution will be constructed using 1,000 bootstrap resamples. Each bootstrap resample will be performed at the patient level, and each resample will have a total sample size equal to the total number of evaluable patients. A two-sided 95% bootstrap confidence interval will be provided.

Subgroup Analysis

The analysis of the primary safety endpoint will be performed on the following the subgroups of patients

- Coronary artery disease patients with cardiomyopathy
- Coronary artery disease patients without cardiomyopathy
- Patients with abnormal baseline ECGs, for each of six abnormal subgroup categories
- Patients with normal baseline ECGs
- Patients with arrhythmias
- Gender
- Patients alerted via Merlin.net and patients alerted via device Patient Notifier

Sample Size

[redacted]

optimize ST feature parameters. The analysis with a 3-month run-in period

4.3.3 Secondary Safety Endpoint

The ST Monitoring Feature will be evaluated by the False Positive Rate (FPR). The False Positive Rate is calculated as the number of false positives per patient-year of follow-up. A False Positive occurs when there is a Type I ST episode that is not followed by a clinical event within 72 hours. Only ST segment shift events that occur beyond the baseline visit will be included in this analysis.

$$\text{FPR} = \frac{\#\text{of false positive events}}{\text{patient years of follow-up}}$$

The hypothesis is formally expressed as follows:

H_0: Expected FPR $\geq$1.9 per patient-year of follow-up
H_a: Expected FPR <1.9 per patient-year of follow-up

The desired outcome is to demonstrate that the False Positive Rate is less than 1.9 events per patient-year. The null hypothesis will be rejected at the 2.5% significance level if the 97.5% upper confidence limit (UCL) for the expected FPR is less than 1.9 per patient-year of follow-up.

Patient Group

All enrolled patients who have a successful implant or system revision and have completed the Baseline visit with the ST Monitoring Feature and Patient Notifier programmed ON will be included in this endpoint.

Further, the analysis population for the secondary safety endpoint will be those subjects with the Fortify® ST (upgraded), Fortify Assura® ST and Ellipse® ST devices. The data from subjects with a Fortify® ST prior to being upgraded will not be included in this analysis.

Analysis

Primary Analysis

The expected FPR will be estimated by the observed FPR. To avoid imbalance in the number of false positives that each patient with false positives contributes, the maximum number of false positives from a patient that will be counted toward meeting the requirement on the number of false positives will be two. In addition, for a single follow up period (i.e. one interrogation and device evaluation to the next), if multiple false positive events occur, only one event will be counted toward the analysis. This will prevent multiple false positives that occur before the physician has the opportunity to evaluate the patient and reprogram the device from contributing to an imbalance in the data. For any patients with more than two false positives their follow up time will be truncated to the date of the second false positive.

The analysis will be carried out where only those false positives counted toward meeting the requirement of number of false positives are included. That is, if a patient has experienced more than two false positives, only the first two false positives of that patient will be included.

The 97.5% upper confidence limit for the expected FPR will be calculated based on the confidence interval calculation of a Poisson rate using the exact method (Ulm, 1990)[6]. The null hypothesis will be rejected at the 2.5% significance level if the 97.5% upper confidence limit is less than 1.9 per patient-year.

Additional Analyses

Empirical analyses will be provided for the false positive rate using

1. the estimator described in the Primary Analysis section, and
2. the estimator that uses all false positive events.

The standard error of these empirical estimators will calculated as the standard deviation of their bootstrap distributions. The bootstrap distributions will be

constructed using 1,000 bootstrap resamples. Each bootstrap resample will be performed at the patient level (in order to preserve the correlation structure between events with a given patient), and each resample will have a total sample size equal to the total number of evaluable patients. The bootstrap distributions will be used to estimate two-sided 95% bootstrap confidence intervals.

Subgroup Analysis

The analysis of the secondary safety endpoint will be performed on the following subgroups of patients

- Coronary artery disease patients with cardiomyopathy
- Coronary artery disease patients without cardiomyopathy
- Patients with abnormal baseline ECGs, for each of six abnormal subgroup categories
- Patients with normal baseline ECGs
- Patients with arrhythmias
- Gender
- Patients alerted via Merlin.net and patients alerted via device Patient Notifier

Sample Size

[redacted]

[redacted]

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

The efficacy endpoint will be evaluated as the sensitivity of the ST Monitoring Feature to detect clinical events. Sensitivity of the ST Monitoring Feature to detect clinical events will be calculated as the number of True Positive events (as defined in section 3.2.3) divided by the total number of ACS clinical events.

$$\text{Sensitivity} = \frac{\#\text{ of TP events}}{\text{Total number of ACS events}}$$

A clinical event is considered to be related to the onset of a Type I ST episode if the clinical event occurs within 72 hours after the onset of a Type I ST episode.

The hypothesis is formally expressed as follows:

H_0: Sensitivity ≤ 50%
H_a: Sensitivity > 50%

The desired outcome is to demonstrate that the sensitivity of the ST Monitoring Feature is greater than 50%. The null hypothesis will be rejected at the 2.5% significance level if the lower bound of the 95% confidence interval for sensitivity is greater than 50%. The lower confidence bound will be calculated using the Wilson score interval method.

Patient Group

All enrolled patients who have a successful implant or system revision, complete the Baseline follow up visit and have the ST Monitoring Feature and Patient Notifier turned ON, and experience clinical events will be included in the evaluation of this study endpoint. Data collection towards the study endpoint will begin after the Baseline visit.

Further, the analysis population for the primary efficacy endpoint will be those subjects with the Fortify® ST (upgraded), Fortify Assura® ST and Ellipse® ST devices. The data from subjects with a Fortify® ST prior to being upgraded will not be included in this analysis.

Analysis

Primary Analysis

The expected sensitivity for ST Monitoring Feature will be estimated by the number of true positive events divided by the total number of ACS events.

The 95% confidence limits will be calculated for sensitivity using the Wilson score interval method[7] for a binomial proportion. The null hypothesis will be rejected if the lower bound of the 95% confidence limit is greater than 50%.

Additional Analysis

An empirical analysis will be provided for the sensitivity of the ST Monitoring Feature to detect clinical events using the estimator described in the Primary Analysis section. The standard error of this empirical estimate will calculated as the standard deviation of a bootstrap distribution. The bootstrap distribution will be constructed using 1,000 bootstrap resamples. Each bootstrap resample will be performed at the patient level (in order to preserve the correlation structure of multiple events within one patient, if the occurs), and each resample will have a total sample size equal to the total number of evaluable patients. A two-sided 95% bootstrap confidence interval will be provided.

Subgroup Analysis

The analysis of the primary efficacy endpoint will be performed on the following subgroups of patients

- Coronary artery disease patients with cardiomyopathy
- Coronary artery disease patients without cardiomyopathy
- Patients with abnormal baseline ECGs, for each of six abnormal subgroup categories
- Patients with normal baseline ECGs
- Patients with arrhythmias
- Gender
- Patients alerted via Merlin.net and patients alerted via device Patient Notifier

Sample Size

[redacted]

[redacted]

The patients to be enrolled in the Analyze ST IDE Study are similar to those [redacted] the total number of patients required to be enrolled is 5,228.

4.5 Overall sample size and data cut-off

The total number of patients required for enrollment in order to satisfy the primary endpoints and the secondary endpoint is driven by the sample size requirement to satisfy the primary efficacy endpoint. Thus the total sample size required for this study is 5,228.

Data collection for the purposes of the FDA market approval application will be considered to be complete when the primary safety endpoint data are available and at least 41 clinical events have occurred.

Following submission of the clinical data, patients will continue to be followed until closure of the study for providing long-term follow up on the Investigational Devices.

4.6 Poolability Analyses

The poolability across sites will be verified for the safety endpoint, percent of patients experiencing a false positive event within 12 months, and for the effectiveness endpoint, sensitivity of the ST Monitoring Feature to detect clinical events. Since it is likely that sites will have a wide variation in the number of patients enrolled (due to differences in site start-up times and differences in patient volumes at the sites), for the purpose of testing poolability, they will be classified into the following categories:

To evaluate poolability across sites, separate generalized linear models will be used for the safety and efficacy endpoints, as follows:

$$\log\left(\frac{p}{1-p}\right) = \textit{site category},$$

where p is the expected proportion of patients experiencing a false positive event within 12 months (safety) or the sensitivity of the ST Monitoring Feature (efficacy). Testing will be conducted at a significance level of 15%. Poolability will be verified for an endpoint if the site category effect is not significant at the 15% significance level.

4.7 Additional Analyses

The following additional data will be collected during the study:

- Demographic variables include: gender, age, ethnicity, cardiomyopathy classification, complete cardiovascular history, arrhythmia history, primary ICD indication, and EF% at the time of enrollment and QRS duration at baseline
- ST Diagnostic Data to include: heart rate at onset of the Type I ST episode, maximum ST shift during the Type I ST episode, Type I ST episode duration, total number of Type I ST episodes detected
- All diagnostic procedures (tests and interventions) stratified by investigator's assessment of whether the procedure would have been performed in presence and absence of ST diagnostic data

- Positive Predictive Value (PPV) of the ST Monitoring Feature
- Negative Predictive Value (NPV) of the ST Monitoring Feature
- Response rates to Patient Notifier and Merlin.net Type I ST Episode detections
- Cardiac medications (including anti-anginal medications) during clinical events
- CPK Isoenzymes, MB fractions and Troponin values collected during clinical events
- Stress test and 12-lead ECG measurements collected during clinical events
- Proportion of patients who have the ST Monitoring Feature turned off at every study visit from the Programming Visit onwards
- Adverse events
- Clinical events
- Spontaneous arrhythmic episodes
- Hospitalizations
- Mortality/Death

4.7.1 Demographic Variables

Demographic variables will be collected for all patients at the time of enrollment and summaries presented. Continuous variables will be presented as mean ± SD, and categorical variables will be tabulated with percentages.

4.7.2 ST Diagnostic Data

ST diagnostic data will be collected and presented for all Type I ST episodes for all patients with the Fortify® ST (upgraded), Fortify Assura® ST and Ellipse® ST devices. Additionally, ST diagnostic data from all patients with the Fortify® ST prior to being upgraded will be collected and presented.

4.7.3 Investigator's Assessment of Procedures Performed

All diagnostic procedures (tests and interventions) stratified by investigator's assessment of whether the procedure would have been performed in presence and absence of ST diagnostic data

4.7.4 Positive Predictive Value (PPV)

The PPV will be calculated as the proportion of true positives (according to section 3.2.3) to the number of all Type I ST episodes (i.e., combination of all true positive and false positive events).

$$PPV = \frac{TP}{TP + FP}$$

4.7.5 Negative Predictive Value (NPV)

The NPV will be calculated as the proportion of true negatives to the combination of false negatives and true negatives (according to section 3.2.3)

$$NPV = \frac{TN}{FN + TN}$$

4.7.6 Response Rates to Patient Notifier and Merlin.net Type I ST Episode Detections

The response rates to Type I ST Episode notifications received through the Patient Notifier and through Merlin.net will be presented.

4.7.7 Cardiac and Anti-Anginal Medications

List of concomitant cardiac and anti-anginal medications will be collected at the Screening visit, Baseline visit and at each clinical event and will be summarized for all patients.

4.7.8 CPK Isoenzymes MB Fractions and Troponin

Cardiac biomarker laboratory tests will be collected during any clinical event as defined by the study protocol. Results will be determined as positive or negative and will be compared to clinical events and to Type I ST episodes.

4.7.9 12-Lead ECG Measurements

12-lead ECG recordings will be collected at the Baseline visit and during any clinically-indicated stress test related to Clinical Events. Results from the 12-lead ECG recordings along with the patient's pertinent medical records will be adjudicated by the CEC and classified as normal or abnormal. All ECG abnormalities will be classified as a preexisting abnormality or as a new finding. An abnormal 12-Lead ECG is defined as having at least one of the following present 1) rhythm other than normal sinus rhythm or sinus tachycardia such as atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, or idioventricular rhythm 2) intermittent or complete conduction abnormalities resulting in widening of the QRS complex (RBBB, LBBB, IVCD, evidence of left ventricular hypertrophy), 3) ST-T wave abnormalities (T wave inversions, J point elevation) 4) frequent PVCs 5) low voltage QRS complexes indicative of dilated cardiomyopathy or COPD, or 6) high voltage QRS complexes indicative of left ventricular hypertrophy. A normal 12-Lead ECG will be defined as one not meeting the criteria for an abnormal ECG.

Results of any stress tests performed will be determined as positive or negative by the site and will be sent to the CEC for further adjudication

4.7.10 Adverse Events

All adverse events will be categorized by the investigator as instructed in Section 6.0 of the investigational protocol. Adverse event evaluation will include the number of patients who experienced any events, the number of events and each event classification.

4.7.11 Clinical Events

Clinical events will be summarized for all patients in terms of the number of events and number of patients. The rate of clinical events will be reported per patient-year of follow-up along with a 95% confidence interval using Ulm's method.

4.7.12 Spontaneous Arrhythmic Episodes

All available spontaneous arrhythmic diagnostic episodes detected by the ICD, as well as the corresponding stored IEGMs, will be retrieved via device interrogation and will be reviewed to evaluate appropriate and inappropriate ICD therapies.

4.7.13 Hospitalizations

Cardiac-related hospitalizations, emergency room visits and surgeries will be summarized using the Kaplan-Meier survival method.

4.7.14 Mortality

The number of deaths will be summarized. The observed mortality rate will be summarized using the Kaplan-Meier survival method.

4.7.15 Re-analysis of Endpoints with a 14-day Threshold

Evaluate primary and secondary endpoints using a 14 day threshold (instead of 72 hours) for associating a Type I ST episode with a true ACS event.

Reference

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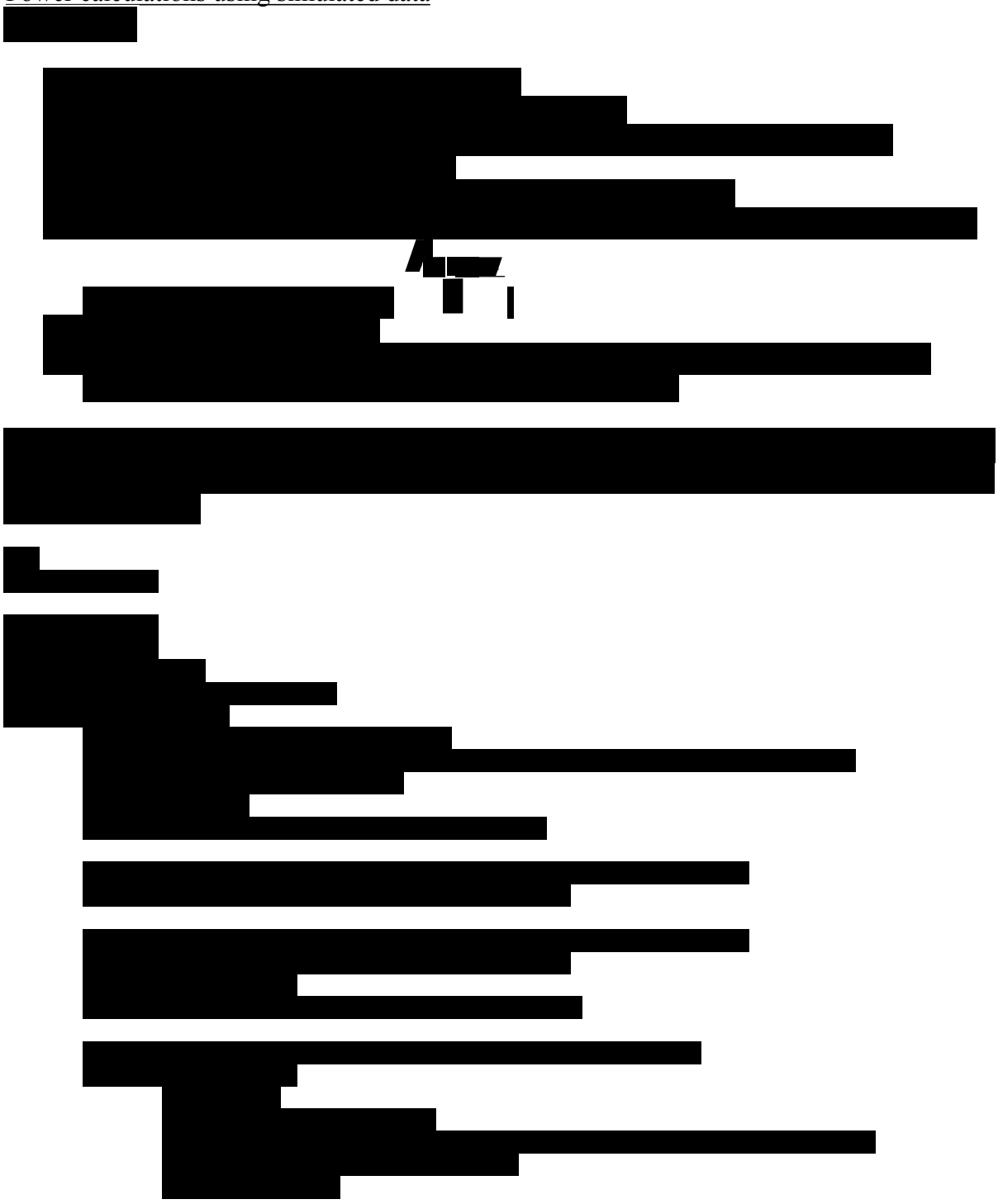
APPENDIX A
Details of Sample Size Calculations

Primary Efficacy Endpoint - False Positive Rate

Power calculations using simulated data

[redacted]



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Secondary Endpoint – Sensitivity of ST Monitoring Feature

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