Long-term monitoring of patients with cardiac amyloidosis with implantable event monitors

NCT# 04421040

August 22, 2023

Long term monitoring of patients with cardiac amyloidosis with implantable event monitors

Principal Investigator	Omar Abou Ezzeddine, M.D., M.S. Department of Cardiology 200 1st St SW. Rochester, MN 55902 (77)4-8846
Co-Investigators	Grace Lin, MD Rosalyn Adigun, MD, PharmD Peter Brady, MB, ChB, MD Yong-Mei Cha, MD Abhishek Deshmukh, MBBS Angela Dispenzieri, MD Martha Grogan, MD Dawn Pedrotty, MD, PhD
Funding Sponsor:	Pfizer 235 East 42nd Street New York, NY 10017 Mayo Clinic 200 First St SW Rochester, MN 55905 Biotronik 6024 Jean Road Lake Oswego, OR 97035-557, USA
Study Product:	Biomonitor 3 (This device is being used in the study but is already FDA approved for this indication. The device is NOT under investigation.)
Protocol Number: (IRBe)	17-006298 **IDE Number:** Not Applicable

Initial version: 4/10/2018 Version 1
Revised: 3/26/2019 Version 2
Revised: 10/16/2019 Version 3
Revised: 1/6/2020 Version 4
Revised: 1/30/2020 Version 5
Revised: 4/30/2021 Version 6
Revised: 6/1/2022 Version 7
Revised: 1/5/2023 Version 8

Revised: 3/21/2023 Version 9
Revised: 08/22/2023 Version 10

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

Study Summary

Title	Long term monitoring of patients with cardiac amyloidosis with implantable event monitors
Running Title	Long term implantable monitors for cardiac amyloidosis.
IRB Protocol Number	17-006298
Phase	Pilot
Overall Study Duration	3 years
Subject Participation Duration	Approximately six months +31 days if removal
Objectives	There are four specific aims. We seek to determine in wild type transthyretin amyloidosis (ATTRwt): **Specific Aim 1**: Burden of conduction system disease and arrhythmias, specifically sinus node dysfunction, high grade heart block, and AF and VA, which will identify those who might benefit from a PPM or ICD **Specific Aim 2**: Mechanism of SCD (asystole, pulseless electrical activity, or sustained VA) and whether this is different in early vs. late stage amyloidosis. **Specific Aim 3**: Risk factors for SCA and more specifically whether bradycardia or VA predict SCD, or whether there are imaging or clinical characteristics that predict SCA **Specific Aim 4**: Utility of long term ECG monitoring in TTR-wt cardiomyopathy
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Patients with ATTRwt cardiac amyloidosis are included in this study.
Device	Biomonitor 3 (Utilized not investigational)
Duration of Exposure	Intended to remain in the body for 6 months pending clinical indications
Reference therapy	No change in standard of care treatment.
Statistical Methodology	Pilot Study

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

Amyloid cardiomyopathy (AC) results from myocardial deposition of amyloid fibrils. The most common forms of amyloidosis associated with cardiac involvement include (1) AL amyloidosis, an immunoglobulin light chain plasma cell dyscrasia; (2) Transthyretin (TTR-m) an autosomal familial amyloidosis resulting from mutant transthyretin and (3) Transthyretin wild type (TTR-wt) amyloidosis, arising from a wild type transthyretin primarily in older individuals (1,2). The onset of a restrictive cardiomyopathy and progressive heart failure is the primary concern in cardiac amyloidosis, but another problematic aspect is infiltration of the conduction system, causing bradycardia, atrial arrhythmias (AF), and sudden cardiac death (SCD) (1,2).

Conduction disease in AC manifests as high-grade atrioventricular (AV) block and sinus node dysfunction (bradycardia, heart rate <35bpm) and standard clinical indications for pacemaker implantation have been applied (1,3); however, many clinicians hesitate to treat with pacemakers (PPM) due to a perceived higher complication rate. Atrial fibrillation also presents several management dilemmas as AV nodal blocking agents typically utilized for rate control may be poorly tolerated, and data on anti-arrhythmic drug therapy and ablation are limited (4,5). A major limitation of ablation is high rates of AF recurrence in amyloidosis (4), hypothesized to occur because the arrhythmia is believed to arise from diffuse amyloid infiltration in the atrial tissue rather than from the pulmonary veins, rendering targeted ablation to isolate the pulmonary veins less effective. Although ventricular arrhythmias are also prevalent, their role in SCD in amyloidosis is also controversial (4,6-9). A longer term monitoring study with implantable loop recorders in a small number of patients with AL amyloidosis has suggested that bradycardia leading to asystole is the more likely culprit, at least in advanced amyloid cardiomyopathy, but it is not clear if this is also true earlier in the disease process or if it applies to TTR-wt (8).

A particular challenge with TTR-wt is the paucity of data pertaining to arrhythmia risk. Much of the published literature, although also limited in scope and sample size, addresses arrhythmia risk only in AL amyloidosis. TTR-wt cardiomyopathy is characterized by a more indolent course compared to AL, and individuals may present with heart block or atrial arrhythmias prior to the onset of advanced heart failure symptoms and often before the diagnosis of TTR-wt cardiomyopathy (1,2). Advancements in imaging techniques such as cardiac magnetic resonance imaging and technetium pyrophosphate scintigraphy that permit earlier and non-biopsy diagnosis of TTR-wt diagnosis have enhanced the diagnosis of TTR-wt cardiomyopathy (10,11). As a result, it appears TTR-wt may be more prevalent than previously known; there is a significant overlap between TTR-wt cardiomyopathy and an ageing population of patients with heart failure with preserved ejection fraction, hypertrophic cardiomyopathy, and those with aortic stenosis undergoing transcatheter valve replacement

(12-14). Therefore arrhythmia risk and management in TTR-wt cardiomyopathy will impact an increasingly growing population of patients, with unique risk factors and management challenges that differ from those with other cardiovascular disease.

One reason that arrhythmia management in amyloidosis has been focused on AL amyloidosis was due to the lack of disease modifying therapies for TTR-wt. The recent availability of disease modifying therapies for TTR amyloidosis that improve both symptoms and mortality also presents an opportunity to impact arrhythmia risk and management (15-17). Previous experiences of implantable cardiac device therapy in amyloid cardiomyopathy for arrhythmia management have suggested that earlier implantation may be associated with superior results (7,18). Whether the current therapies targeted towards stabilization and knockdown of circulating TTR will impact existing conduction disease is less clear, but these therapies may halt, delay or prevent onset of more severe disease that would not be amenable to treatment and could influence mortality. The main objective of this study is to identify TTR-wt cardiomyopathy patients at risk for bradycardia or SCD who may benefit from PPM or implantable cardioverter defibrillators (ICD), and to determine whether monitoring of TTR-wt patients undergoing treatment with disease modifying therapies will identify the subgroup of patients who will benefit most from PPM or ICD.

1.2 Device

The device used in this protocol is NOT investigational. Biomonitor 3 is FDA and available on all markets for monitoring of arrhythmias. This protocol will use the device as FDA approved.

Briefly, The Biomonitor 3 is indicated to detect the following cardiac arrhythmias:

- atrial fibrillation
- bradycardia,
- sudden rate drop,
- high ventricular rate (HVR),
- asystole

The Biomonitor 3 is indicated for use in:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms that may suggest a cardiac arrhythmia
- The device has not been tested for and it is not intended for pediatric use

1.3 Clinical Data to Date

Pilot Study Data submitted to FDA resulting in FDA approval of the Biomonitor implantable loop recorder (ILR) device

The objective of this pilot study was to provide clinical data of the insertion procedure and the sensing quality of BIOTRONIK's second generation of ILR, the BioMonitor 2, a device which is inserted subcutaneously. Data of 30 patients from 5 Australian clinical sites from December 18, 2014 through July 06, 2015 were included. The most common indications for

insertion of the BioMonitor 2 were syncope and symptomatic or asymptomatic atrial fibrillation. The published results demonstrate safety and efficacy of the insertion procedure and the study device.

The next generation device, the Biomonitor 3 device was FDA approved in 2019 and represents an advancement from its predecessor. It is 60% smaller than the Biomonitor 2 device and is preloaded into a single piece injection tool to permit less invasive and easier insertion, including office settings. Injectable implantable loop recorders which can be inserted subcutaneously are the industry standard. Device recordings offer increased signal quality over its predecessor, the Biomonitor 2.

1.4 Study Rationale and Risk/Benefits

1.4.1 Study Rationale

TTR-wt cardiomyopathy has been considered a life limiting, if indolent, and untreatable cause of heart failure in older individuals. For this reason, clinicians have hesitated to treat potentially life threatening arrhythmias, or to consider implantation of cardiac devices (PPM or ICD) which may improve symptoms and impact mortality. The recent availability of disease modifying therapies ushers in a new era of treatment strategies which improve both mortality and morbidity. The goal of the study is to identify patients who would also benefit from treatment of arrhythmias, and who might otherwise have succumbed to complications from arrhythmias, including stroke, sudden cardiac death, or injury from syncope due to bradycardia.

Implantable loop recorders have been used successfully to monitor for arrhythmia burden and to identify causes of cryptogenic syncope and stroke in patients with cardiovascular disease (19,20). The devices can be implanted at low risk and with local anaesthesia and can be inserted in an office setting, and remaining in situ for up to 3 years to permit long term monitoring (21). The device are explanted at the time of battery expiration. Miniaturized implantable loop recorders have been used to document mechanisms of sudden death in late stage AL amyloidosis but have not been routinely utilized especially in TTR-wt (8). Given the perceived high risk for arrhythmias and the lack of robust data on arrhythmia burden, amyloid cardiomyopathy would seem an ideal population to monitor with implantable long-term loop recorders.

An observation from the recently published Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) was the subgroup analysis suggesting greater benefit in less severe heart failure (17,22). Arrhythmia risk (AF, heart block, and cardiac arrest) might be different in patients with earlier stages of the disease, and if treatment with tafamidis might prevent further progression of conduction system disease and arrhythmia burden. The current study proposed is a pilot study and will not be powered to ascertain the effects of tafamidis on arrhythmia burden in different stages of disease, but observations from the study will provide preliminary data for future and necessary prospective monitoring studies.

Despite high risk of SCD, appropriate risk stratification in amyloid cardiomyopathy is lacking. Traditional risk stratification with decreased ejection fraction (<35%) commonly

applied to ischemic cardiomyopathy is not useful in amyloid cardiomyopathy where decreased ejection fraction is a late finding and indicative of advanced disease and increased mortality due to low output and pump failure. Recent studies have cast increasing doubt on the wisdom of generalizing decreased ejection fraction as a risk stratifier for SCD in patients with heart failure due to other causes, specifically those with non-ischemic cardiomyopathies(23) and heart failure with preserved ejection fraction (24). At this time, patients with amyloid cardiomyopathy are without appropriate risk stratification metrics and are at risk for inadequate treatment and at increased risk for SCD.

The prognostic value of non-sustained VA, another traditional risk factor for SCD in ischemic cardiomyopathy, is also controversial in amyloid cardiomyopathy. Long term outpatient monitoring of both supraventricular and ventricular arrhythmias for prognostic implications in relation to other diagnostic modalities is instrumental in understanding the disease process and providing appropriate therapy.

Currently, the balance of data does not support ICD implantation in amyloid cardiomyopathy (7). However, some studies have demonstrated that ventricular arrhythmias resulting in SCD can be successfully treated with defibrillation, hypothesizing that this treatment may be more successful in earlier stage disease (8,26,27). SCD in late stage disease has been hypothesized to be due to electromechanical dissociation or bradycardia mediated asystole for which an ICD would not be beneficial (25)(8,18). The Mayo clinic staging system based on cardiac biomarkers has been validated and is used to stratify severity of disease (early vs late stage) in TTR-wt cardiomyopathy. The reported 4 year survival estimates of patients with Mayo stage I (TnT <0.05ng/ml and NT BNP <3000 pg/mL), II (either TnT >0.05 ng/ml or NT BNP >3000 pg/mL), and III (TnT >0.05 ng/ml and NT BNP >3000 pg/mL) TTRwt amyloidosis was 57%, 42%, and 18%, respectively (28). Those patients with advanced amyloid cardiomyopathy may have estimated survival less than a year due to heart failure and should be excluded from ICD whereas those with earlier stage may still have added survival benefit. We hypothesize that the occurrence and treatibility of ventricular arrhythmias is dependent on disease progression and may be a phenomena of earlier stage disease. Monitoring at all stages of CA disease to understand arrhythmia risk at each stage is instrumental in understanding the true prevalence and treatment of arrhythmias.

Patients with CA and conduction disease undergo pacemaker implantation for standard guideline criteria. However, bradycardia has been implicated as a mechanism for SCD. Bradycardia leading to asystole has been postulated to be a pre-terminal event reflecting an irreversible sick myocardium (8). A second hypothesis is that the reduced cardiac output associated with bradycardia might be sufficient to induce global ischemic stunning of the heavily infiltrated ventricular myocardium resulting in decompensation and pulseless electrical activity (PEA) arrest(8). In a study of AL amyloidosis patients monitored with ILR, one patient with severe bradycardia who underwent early pacemaker implantation survived. Therefore, it is possible that prophylactic pacemaker implantation into healthier myocardium may prevent SCD due to bradycardia, and treatment with disease modifying therapies can prevent further disease progression. Furthermore, a recent study of prophylactic pacemaker insertion in patients with TTR patients with a genetic variant associated with increased risk of conduction disorders showed a reduction in major cardiac

events over a 45 month follow up (29). The proposed study would permit improved understanding of the initiation of bradycardia, correlating to stage of disease and clinical imaging; helping to further elucidate the pathophysiology of bradycardia and heart block in CA.

1.4.2 Anticipated Risks

Biomonitor 3 is an FDA approved device and will be used in accordance with approved FDA usage. Risks have already been assessed for this device and deemed acceptable for this medical application.

Risks for the BioMonitor 3 are minimal but include risk of bleeding and discomfort on insertion, infection, and malfunction. The BioMonitor 3 demonstrated excellent sensitivity for all types of arrhythmias, combined with a low false detection rate.

List of Anticipated Risks:

- Discomfort at time of insertion
- Infection
- Bleeding

False detection is a minimal risk. The BioMonitor 3 has demonstrated excellent sensitivity for all types of arrhythmias, combined with a low false detection rate.

1.4.3 Potential Benefits

We hypothesize that arrhythmogenesis and SCD risk in this population is influenced by CA stage rather than reduced left ventricular ejection fraction, which is a marker of late disease and increased mortality due to heart failure, bradycardia, or asystole, rather than SCD due to VA. The purpose of this study is to identify TTR-wt cardiac amyloidosis patients at risk for bradycardia or SCD due to VA who may benefit from PPM or ICD, and to determine whether monitoring may be appropriate as standard of care to identify the subgroup of patients who will benefit from PPM or ICD.

2 Study Objectives

Listed below are the specific aims/objectives for this study.

Specific Aim 1: Burden of conduction system disease and arrhythmias, specifically sinus node dysfunction, high grade heart block, and AF and VA, which will identify those who might benefit from a PPM or ICD
Specific Aim 2: Mechanism of SCD (asystole, pulseless electrical activity, or sustained VA) and whether this is different in early vs. late stage amyloidosis.
Specific Aim 3: Risk factors for SCA and more specifically whether bradycardia or VA predict SCD, or whether there are imaging or clinical characteristics that predict SCA
Specific Aim 4: Utility of long term ECG monitoring in TTR-wt cardiomyopathy

2.1 Primary Objective

This is a Pilot Study designed to support future expanded Pivotal Studies of the device. The study is designed to assess arrhythmic events using the implantable cardiac monitor, Biomonitor 3, in subjects presenting to the clinic with TTR-wt cardiac amyloidosis.

2.2 Secondary Objective

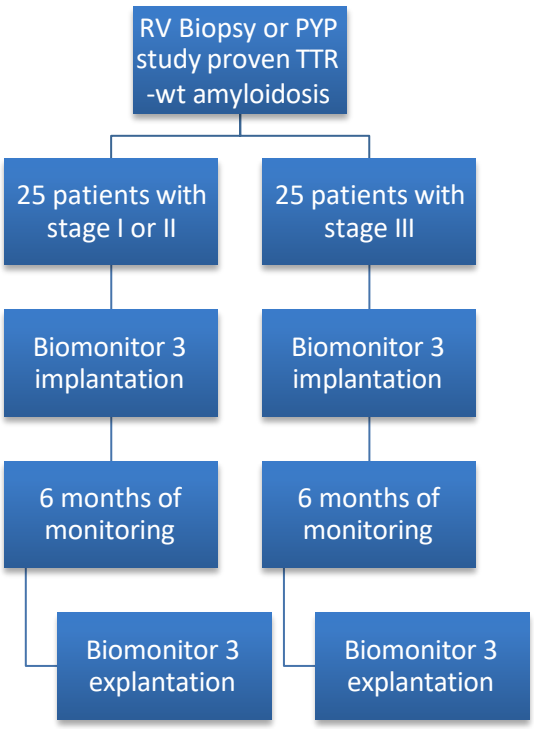
The secondary goal is to assess arrhythmogenesis in relation to stage of cardiac amyloidosis

3 Study Design

3.1 General Design

This is a pilot study of 50 patients to monitor arrhythmogensis for six months with +31 days post implantation in patients TTR-wt cardiac amyloidosis proven by endomyocardial biopsy or technetium pyrophosphate scintigraphy. Study staff will provide continuous monitoring of the ILR.

The general design is outlined below:



3.2 Primary Study Endpoints

1. Sudden cardiac death (including resuscitated cardiac arrest).

2. Syncope due to heart block or sinus node dysfunction requiring pacemaker

3.3 Secondary Study Endpoints

1. All-cause mortality: with a focus on HF deaths and bradycardia/PEA
2. PPM implantation and indication, frequent of pacing required, and if BIV pacing is needed
3. ICD implantation and indication, frequency of shocks and if appropriate vs inappropriate and if successful defibrillation occurred
4. Frequency of NSVT and predictability with other ventricular arrhythmias and sudden cardiac death
5. Frequency of atrial flutter or fibrillation and predictability with other arrhythmias including predictability of ventricular arrhythmias and sudden cardiac death

4 Subject Selection, Enrollment and Withdrawal

The target population is patients with TTR-wt cardiac amyloidosis. We plan to enroll 50 patients in this pilot study. Specifically, we will enroll 25 patients diagnosed with stage I or stage II disease and 25 with stage III disease.

Patients will be screened and recruited from the Amyloidosis Clinics, heart failure clinics and respective hospital services.

4.1 Inclusion Criteria

1. Cardiac biopsy or technetium pyrophosphate scintigraphy confirmed patients
2. Stage I, II, and early and late stage III in numbers as described, irrespective of EF or NYHA functional class
3. Patients aged 18 -85, both genders and of all races and ethnicities.
4. Patients must be competent to give informed consent.
5. Patients must be able to have the Biomonitor 3 implanted.
6. Amyloid stages I-III patients with existing implantable cardiac devices such as pacemakers or defibrillators

4.2 Exclusion Criteria

1. Significant coronary artery disease > 75% luminal stenosis in at least 1 epicardial vessel (by cardiac catheterization or coronary computed tomography), or history of myocardial infarction or coronary revascularization.
2. Congenital heart disease.
3. Pregnant patients
4. Patients whose heart failure is felt to be secondary to primary valvular disease (≥ moderate/severe mitral regurgitation), uncorrected thyroid disease, obstructive or hypertrophic cardiomyopathy, pericardial disease or a systemic illness.
5. Absolute contraindications to cardiac MRI (such as renal failure with GFR<30%).
6. Unwilling or unable to provide informed consent.
7. Patients with other life threatening diseases that would likely decrease their life expectancy over the next four years.
8. Patients who are post cardiac transplant.
9. Difficulty to attend the follow-up schedule due to a history of medical noncompliance, difficulty, or unwillingness to return to the study center for follow up.
10. Evidence of ongoing bacteremia or sepsis preventing implantation of a device.
11. Unwilling or able to have the Biomonitor 3 interrogated

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be screened and recruited from the from the Amyloidosis Clinics, heart failure clinics and respective hospital services. Patients will receive standard of care therapy including staging with cardiac biomarkers. We will recruit 25 patients with stage I or II and 25 patients with stage III. Prior to time of recruitment, inclusion and exclusion criteria will be reviewed for each patient.

There are no known contraindications for the insertion of the BioMonitor 3. However, the patient's particular medical condition may dictate whether or not a subcutaneous, chronically inserted device can be tolerated.

Patients will have the option to leave the device in situ for the lifetime of the device . If opting for the full battery lifetime, the patient/insurance company would be responsible for the continued monitoring after the 6 month study period and the explantation of the device at battery end of life.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients may withdraw at any time from the study. Reason for withdraw may include but are not limited to adverse events, progression of disease requiring withdrawal or simply the patient's decision to withdraw.

If a subject does withdraw, that subject will be replaced according to the originally assigned group to permit enrollment of 50 patients complete the study.

Patients may be withdrawn from the study by the investigators if an insertable monitor requires emergent removal. Reasons for removal include, but are not limited to: patient death; loss of sensing; inability to program/interrogate the inserted monitor; infection, battery end of life (normal or premature); system upgrade; physician preference for another insertable monitor model; and/or other reason(s) which may or may not be known to the insertable monitor manufacturer. Complications related to other portions of the insertable monitor system (i.e., patient) may also result in insertable monitor removal. The table below summarizes some of the more common reasons for insertable monitor removal.

Source	Cause	Possible Effect
Battery	Premature depletion or other cause(s) resulting in excessive battery current drain.	Inability to program/interrogate; sensing difficulty.
Circuitry	Electrical parameter changes due to shorts, opens, or component parametric drift Electromagnetic Interference (EMI) from large power tools, industrial equipment, electrocautery, defibrillation, radiation therapy, RF ablation therapy, etc.	Reversion to "Elective Replacement" or electrical reset parameters; inability to program/ interrogate; other damage to circuit components resulting in permanent or temporary parameter changes.
Patient	Normal medical complication	Infection
	Body rejection phenomena	Fluid accumulation; migration; erosion.
	Physician preference	Upgrade to an implantable cardiac pacemaker or implantable cardioverter defibrillator.

If the device is removed due to need for a pacemaker or implantable cardioverter defibrillator the patient will continue to be monitored via the pacemaker or defibrillator as per clinically indicated standard of care monitoring protocol and intervals.

If a subject chooses to withdraw from the study, and requests the monitor to be explanted prior to the end of the 6 month study monitoring period, there will be no further follow up.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, follow-up and survival data on such subjects throughout the protocol defined follow-up period will still need to be collected if possible. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study device. If a subject withdraws consent to participate in the study, for subject safety reasons, attempts will be made to obtain permission to collect follow up information whenever possible.

4.5 Description

Biomonitor 3 is a programmable, subcutaneous insertable monitor able to record subcutaneous ECGs (sECGs) and other physiological parameters.

The Biomonitor 3 is designed to automatically record the occurrence of arrhythmias in a patient. Arrhythmia may be classified as atrial fibrillation (AF), bradyarrhythmia, asystole, sudden rate drop, or high ventricular rate. In addition, the Biomonitor 3 can be activated by the patient to record cardiac rhythm during symptomatic episodes.

The Biomonitor 3 system consists of three main components:

1. Biomonitor 3 insertable cardiac monitor - The Biomonitor 3 is a small, leadless device that is typically inserted under the skin, in the chest. The device uses two electrodes on the body of the device to continuously monitor the patient's subcutaneous ECG. The device memory can store up to 30 min of subcutaneous ECG (sECG) recordings from automatically detected arrhythmias and up to 30 min of sECG recordings from patient-triggered episodes. When a patient experiences symptoms, the sECG recordings can be manually triggered by placing the Remote Assistant III over the Biomonitor 3. The insertable monitor is provided preloaded in an insertion tool. An incision tool is also provided.

   Note - The Biomonitor 3 subcutaneous ECG may differ from a surface ECG due to differences in electrode separation and device placement in the body. Biomonitor 3 detects a subcutaneous ECG from a pair of electrodes. These signals are filtered in two different ways. For detection of QRS complexes, the signals are filtered with a passband of 10-40 Hz in order to suppress T-waves, artifacts, and baseline drift at low frequencies, and myoptentials and EMI at high frequencies. The resulting signal is appropriate for QRS detection as other components of the signal have been suppressed. This signal naturally does not have a typical ECG morphology due to the bandpass. For waveform display (real-time streaming sECG with the physician's programmer and snapshots for review by the physician), a different passband is utilized to retain signal features that may have diagnostic value. This passband is 0.5 – 40 Hz, which is designed to retain morphological features of a typical ECG while still rejecting large low frequency artifacts and baseline drift.

2. BIOTRONIK Renamic / ICS 3000 Programmer – The programmer is used to set up the Biomonitor 3 to detect arrhythmias. It also allows you to view, save, or print the stored information.

3. BIOTRONIK CardioMessenger® Smart is a telemetry patient device that forwards the data from the Biomonitor 3 to BIOTRONIK's Home Monitoring Service Center.

Biomonitor 3 may be used with BIOTRONIK Home Monitoring® technology, which is an automatic, wireless, remote monitoring system for management of patients with insertable cardiac monitors. When active, Home Monitoring enables the exchange of information about a patient's cardiac status from the implant. The information is transmitted to the Home Monitoring Service Center (HMSC), where the physician may log in to review. The HMSC can be used to provide the physician with advanced reports from the implanted device and process them into a graphical and tabular format. This information may help the physician optimize the therapy process, possibly providing earlier notification of clinically relevant events to help guide future therapy.

- BIOTRONIK conducted the TRUST study to evaluate the safety and effectiveness of Home Monitoring. With the TRUST study, BIOTRONIK was able to show the following with regards to Home Monitoring:

- BIOTRONIK Home Monitoring information may be used as a replacement for device interrogation during in-office follow-up visits.
- A strategy of care using BIOTRONIK Home Monitoring with office visits when needed has been shown to extend the time between routine, scheduled in-office follow-ups of BIOTRONIK implantable devices in many patients. Home Monitoring data is helpful in determining the need for additional in-office follow-up.
- BIOTRONIK Home Monitoring provides early detection of arrhythmias.
- BIOTRONIK Home Monitoring provides early detection of silent, asymptomatic arrhythmias.
- Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring allows for earlier intervention than conventional in-office follow-ups.
- BIOTRONIK Home Monitoring allows for improved access to patient device data compared to conventional in-office follow-ups since device data is automatically collected and reported on a daily basis.
- The implanted device's Home Monitoring function can be used for the entire operational life of the implanted device (prior to ERI).
- NOTE: When ERI mode is reached, this status is transmitted and Home Monitoring® will be discontinued after two weeks.

Electromagnetic Interference (EMI) - Precautions for EMI interference with the Biomonitor 3 insertable cardiac monitors including cellular telephones, electronic article surveillance systems, and others.

Use in Cellular Phone Restricted Areas - The mobile patient device (transmitter/receiver) should not be utilized in areas where cellular phones are restricted or prohibited (i.e., commercial aircraft).

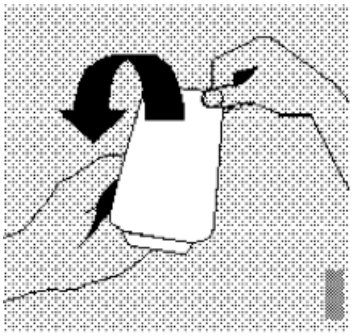
Elective Replacement Indicator (ERI) - When ERI mode is reached, this status is transmitted. Home Monitoring data transmissions will continue for another 2 weeks. After 2 weeks, data will no longer be transmitted to the Service Center.

Communication Loss - A system alert appears in the physician's queue on the Home Monitoring website if no data transmissions occur for a period of time programmed by the user. You may configure alerts so that an SMS, fax and/or e-mail message is sent to the physician regarding the communication loss. If no data transmissions have been received by HMSC after 90 days, the patient will be deactivated. In the event of sustained communication loss, an in-office follow-up visit is recommended.

4.6 Preparation and Administration/Implantation and Explantation of Device

Preparation of Device

The Biomonitor 3 is preloaded in the insertion tool and is packaged with an incision tool in a single container sterilized with ethylene oxide. The device can be implanted in an office setting and all implantations for the study will be performed in the Clinical Research Trials Unit (CRTU). The implantation procedure is performed with injection of a local anesthetic (lidocaine). Conscious sedation is not required.



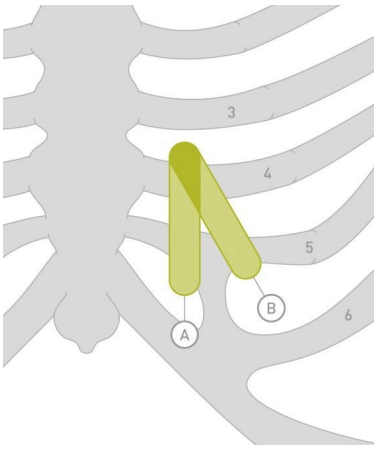
Peel off the sealing paper of the outer container as indicated by the arrow.

Insertion

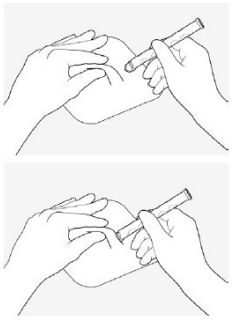
The FIT OneStep Tool allows an “injection-like” insertion of the implant using a single tool. It is used for forming the device tunnel and subsequent subcutaneous delivery of the Biomonitor 3 implant. The Biomonitor 3 implant is provided preloaded into the blue tunneling end of FIT OneStep tool,
which has a rigid clam-shell design. There is a small window over the BIOMONITOR III implant to allow the physician to see the implant in the FIT OneStep tool. The incision tool and FIT OneStep tool are intended for single use.

Incision and FIT OneStep tools

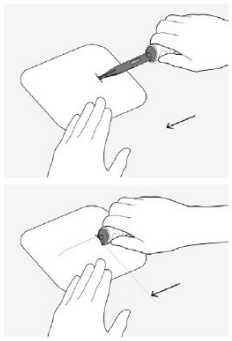
Biomonitor 3has been developed to be inserted in a close-fitting subcutaneous tunnel, preferably in or around the left side of the chest. Recommended locations are those areas close to the heart where the implant will be exposed to minimal movement from body positional changes or from arm movement. Suitable implant locations are shown below. In position A, a location between the suprasternal notch and the left nipple is shown. Position B shows an implant location of approximately 45° with respect to the midline. The choice of placement location is to be decided by the physician, on the basis of individual patient anatomy and comfort, as well as cosmetic considerations. The insertion process consists of four (4) intuitive steps: Incision, Tunneling, Unlocking and Retraction



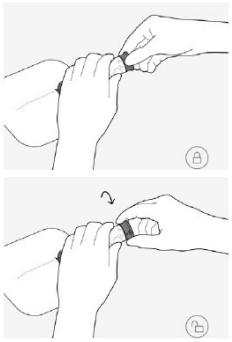
Two recommended positions for the placement for Biomonitor 3



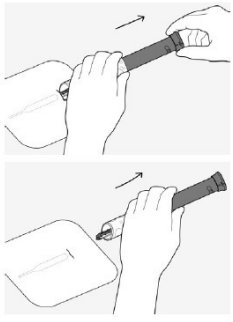
Step 1
Local anesthetic agent is injected at the selected anatomical position, both along the incision line, and along the length of the planned tunnel. After an appropriate delay to allow the local anesthetic agent to take effect, the incision tool is used to make an incision through the skin. The physician is advised to consider the patient's anatomy when making the incision.



Step 2
The FIT OneStep Tool with the preloaded BIOMONITOR III implant is then advanced within a sub-dermal plane until the skin reaches the insertion stopping point, to create a tunnel for the BIOMONITOR III implant.



Step 3
Once the tunneling part of the tool is fully inserted, the knob at the proximal end of the handle is turned counter-clockwise to the unlocked icon.



Step 4
Holding the outer white portion of the handle stationary against the incision, retract the blue inner portion by pulling back and away from the white portion. The implant will remain in place within the tunnel.

ICM insertion has been associated with a small risk of device migration and loss through the incision. To help promote healing and device integrity, closure of the incision, in addition to skin dressing, should be considered for at risk patients. The protection of the wound from environmental influences finalizes the insertion procedure for BIOMONITOR III.

Biomonitor 3 insertion procedure

Explantation

Explantation will be performed in the CRTU or the HRS Lab. Local anesthetic is injected into the previous incision site. Gentle traction is applied to the device and the device is removed.

4.7 Subject Compliance Monitoring

All patients will undergo Home Monitoring of their device. By default, the Biomonitor 3 will transmit all data and a daily trend report between 1:00 A.M. and 2:00 A.M. daily. BIOTRONIK's Home Monitoring system is also designed to notify clinicians in less than 24 hours of changes to the patient's condition or status of the inserted device. Updated data may not be available if:

- The patient's CardioMessenger is off or damaged and is not able to connect to the Home Monitoring Service Center.
- The CardioMessenger cannot establish a connection to the inserted device.
- The telephone and/or Internet connection do not operate properly
- The Home Monitoring Service Center is off-line (upgrades are typically completed in less than 24 hours)

These updates will help to assist the subject to make the necessary changes so that data can be transmitted and they are not lost to follow up.

4.8 Prior and Concomitant Therapy

Patients may continue on standard of care medical therapy for amyloidosis and any other medical therapy needed.

Patients enrolled in the study with an implanted Biomonitor 3 need careful assessment prior to undergoing one of the following procedures. A detailed analysis of the advantages and risks should be made. Cardiac activity during one of these procedures should be confirmed by continuous monitoring of peripheral pulse or blood pressure. Following the procedures, insertable cardiac monitor function must be checked.

Therapeutic Diathermy Equipment - Use of therapeutic diathermy equipment is to be avoided for insertable cardiac monitor patients due to possible heating effects of the insertable cardiac monitor and at the implant site. If diathermy therapy must be used, it should not be applied in the immediate vicinity of the insertable cardiac monitor. The patient's peripheral pulse should be monitored continuously during the treatment.

Transcutaneous Electrical Nerve Stimulation (TENS) - Transcutaneous electrical nerve stimulation may interfere with insertable cardiac monitor function. If necessary, the following measures may reduce the possibility of interference:

Place the TENS electrodes as close to each other as possible.

Place the TENS electrodes as far from the insertable cardiac monitor as possible.

Monitor cardiac activity during TENS use.

Defibrillation - The following precautions are recommended to minimize the inherent risk of insertable cardiac monitor operation being adversely affected by defibrillation:

The paddles should be placed anterior-posterior or along a line perpendicular to the axis formed by the insertable cardiac monitor

The energy setting should not be higher than required to achieve defibrillation.

Radiation - Insertable cardiac monitor electronics may be damaged by exposure to radiation during radiotherapy. To minimize this risk when using such therapy, the insertable cardiac monitor should be protected with local radiation shielding.

Lithotripsy - Lithotripsy treatment should be avoided for insertable cardiac monitor patients since electrical and/or mechanical interference with the insertable cardiac monitor is possible. If this procedure must be used, the greatest possible distance from the point of electrical and mechanical strain should be chosen in order to minimize a potential interference with the insertable cardiac monitor.

Electrocautery - Electrocautery should never be performed within 15 cm (6 inches) of an insertable cardiac monitor because of the danger of damaging the insertable cardiac monitor. When possible, a bipolar electrocautery system should be used.

Transurethral resection of the prostate - It is recommended that the cautery ground plate be placed under the buttocks or around the thigh, but not in the thoracic area where the current pathway could pass through or near the cardiac monitor.

Importantly, the device is **MR Conditional -** The cardiac monitor is labeled and certified MR conditional.

The following requirements must always be fulfilled in order to perform an MR scan using BIOTRONIK's BioMonitor 3:

1. There are no other active or abandoned cardiac implants (e.g., lead extensions, lead adapters or abandoned leads) in the patient's body.
2. Other active or passive implants are permitted if they are identified as MR conditional by the manufacturer. NOTE: An MRI scan is permitted only if the product-specific conditions are met for all implants and if no metal insertable device longer than 5 cm is in the vicinity of the BIOTRONIK cardiac monitor within a distance of less than 4 cm.
3. The device is located in the patient's chest area.

The MRI scanner has to meet the following conditions:

1. Use of a clinical MRI system with a cylindrical bore and a static magnetic field strength of:
    a. 1.5 Tesla (for BioMonitor and BioMonitor 3) or 3.0 Tesla quadrature transmit coils
    b. only (for BioMonitor 2).
2. The slew rate of the MRI scanner's gradient fields should not exceed 200 T/m/s per axis.
3. For the head and the extremities, local transmitter and receiver coils are approved for use in addition to the local receiver coils.
4. Only local receiver coils may be used for the thorax.

5. Maximum spatial gradient of the static magnetic field specification must be ≤ 100T/m (10,000 gauss/cm).
6. Under worst case conditions, the BioMonitor 3 is expected to produce a maximum temperature rise of <4.5° C after 30 minutes of continuous scanning.
7. Image artifact and distortion can result from the presence of the BioMonitor 3 device within the field of view. Image artifact and distortion resulting from the presence of the device within the field of view must be considered when selecting the field of view and imaging parameters. These factors must also be considered when interpreting the MRI images.

The following conditions must be met during the MR scan:

1. The MR scan should be performed with the patient in supine position.
2. The mean specific absorption rate (SAR) for the whole body as displayed by the MRI scanner must not exceed 4.0W/kg.
3. The head absorption rate displayed by the MR scanner must not exceed 3.2 W/kg.

Environmental factors

The operation of any insertable cardiac monitor can be affected by certain environmental sources generating signals that resemble cardiac activity. In some cases the disturbance sources can couple sufficient energy to damage the insertable cardiac monitor.

BIOTRONIK insertable cardiac monitors have been designed to significantly reduce susceptibility to disturbance sources. However, due to the variety and complexity of sources creating interference, there is no absolute protection against disturbance sources. Generally, it is assumed that disturbance sources produce only minor effects, if any, in insertable cardiac monitor patients. If the patient presumably will be exposed to one of the following environmental conditions, then the patient should be given the appropriate warnings.

The following equipment (and similar devices) may affect normal insertable cardiac monitor operation: electric arc welders, electric melting furnaces, radio/television and radar transmitters, power generating facilities, high voltage transmission lines, electrical ignition systems (also of gasoline powered devices) if protective hoods, shrouds, etc., are removed, electrical tools, anti-theft devices of shopping centers and electrical appliances, if not in proper condition or not correctly grounded and encased.

Patients should exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. Some potential EMI sources include:

High Voltage Power Transmission Lines - High voltage power transmission lines may generate enough EMI to interfere with insertable cardiac monitor operation if approached too closely.

Home Appliances - Home appliances normally do not affect insertable cardiac monitor operation if the appliances are in proper condition and correctly grounded and encased. There are reports of insertable cardiac monitor disturbances caused by electrical tools and by electric razors that have touched the skin directly over the insertable cardiac monitor.

Communication Equipment - Communication equipment such as microwave transmitters, linear power amplifiers, or high-power amateur transmitters may generate enough EMI to interfere with insertable cardiac monitor operation if approached too closely.

Commercial Electrical Equipment - Commercial electrical equipment such as arc welders, induction furnaces, or resistance welders may generate enough EMI to interfere with insertable cardiac monitor operation if approached too closely.

Electrical Appliances - Electric hand-tools and electric razors (used directly over the skin of the insertable cardiac monitor) have been reported to cause insertable cardiac monitor disturbances. Home appliances that are in good working order and properly grounded do not usually produce enough EMI to interfere with the insertable cardiac monitor operation.

Electronic Article Surveillance (EAS) - Equipment such as retail theft prevention systems may interact with the insertable cardiac monitor devices. Patients should be advised to walk directly through and not to remain near an EAS system longer than necessary.

Cell Phones - Recent studies have indicated there may be a potential interaction between cellular phones and insertable cardiac monitor operation. Potential effects may be due to the radio frequency signal when the phone is within close proximity (within 6 inches [15 centimeters]) to the insertable cardiac monitor. Based on testing to date, effects resulting from an interaction between cellular phones and the insertable cardiac monitors have been temporary. Simply moving the phone away from the inserted device will return it to its previous state of operation.

To minimize such interactions, patients having an inserted cardiac monitor who operate a cellular phone should:

- Maintain a minimum separation of 6 inches (15 centimeters) between a hand-held personal cellular phone and the inserted device. Portable and mobile cellular phones generally transmit at higher power levels compared to hand held models. For phones transmitting above 3 watts, maintain a minimum separation of 12 inches (30 centimeters) between the antenna and the inserted device.
- Patients should hold the phone to the ear opposite the side of the inserted device. Patients should not carry the phone in a breast pocket or on a belt over or within 6 inches (15 centimeters) of the inserted device as some phones emit signals when they are turned ON but not in use (i.e., in the listen or standby mode). Store the phone in a location opposite the side of the cardiac monitor.

4.9 Packaging and Labeling

The insertable monitor is shipped in a cardboard box, equipped with a quality control seal, and product information label. The label contains the model specifications, technical data, serial number, expiration date, and sterilization and storage information of the insertable monitor. The box contains a double container with the insertable monitor and product documentation.

The insertable monitor and its accessories have been sealed in a container and gas sterilized with ethylene oxide. To assure sterility, the container should be checked for integrity prior to opening. If a breach of sterility is suspected, return the insertable monitor to BIOTRONIK.

The insertable monitor is packaged in two plastic containers, one within the other. Each is individually sealed and then sterilized with ethylene oxide. Due to the double packing, the outside of the inner container is sterile and can be removed using standard aseptic technique and placed on the sterile field.

4.10 Receiving, Storage, Distribution and Return

4.10.1 Receipt of Devices

The Biomonitor 3 devices will be delivered directly to the study staff where they will be stored and inventoried. Biotronik will ship the devices directly to the study staff. The devices will be stored in the study staff offices. Study staff will record receipt in the device accountability log.

The designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable devices in a given shipment will be documented in the study files. The sponsor-investigator will notify the supplier immediately of any discrepancies, damaged or unusable products.

4.10.2 Storage

Storage (temperature) - Recommended storage temperature range is -10° to 45°C (14°-113°F). Exposure to temperatures outside this range may result in insertable cardiac monitor malfunction.

Temperature Stabilization - Allow the device to reach room temperature before programming or implanting the device. Temperature extremes may affect the initial device function.

Storage - Store the device in a clean area, away from sources of disturbance to avoid damage to the device.

4.10.3 Distribution of Study Device

Biotronik will be providing the devices for implantation and no less than 5 devices will be stored for this specifical study protocol. Regular device inventory audits will be performed. This is done to ensure a sufficient supply for the study as well as ensure proper tracking of devices received and used.

4.10.4 Return or Destruction of Device

The device will not be used if the packaging is wet, punctured, opened or damaged because the integrity of the sterile packaging may be compromised. The device will not be used if an unpackaged insertable cardiac monitor is dropped onto a hard surface, The device will not be used if there noted damage on opening the package, or if the device is expired. All devices will be returned to Biotronik in exchange for a functional device. All device serial numbers will be recorded on implanation.

At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the sponsor-investigator will be notified and an investigation will be conducted to determine the cause of the discrepancy. Devices destroyed on site will be documented in the study files.

5 Study Procedures

Arrhythmias will be assessed via home monitoring through the Biomonitor 3 device. Superventricular tachycardia (SVT), ventricular arrhythmias (VA), bradycardia (<35bpm), heart block and atrial arrhythmias are considered of interest.

Home Monitoring for arrythmias

Telemetry tracings from the implantable monitor will be reviewed monthly or whenever an event occurs and/or a patient transmits data due to symptoms via remote assistance.

Default transmission is data sent daily between 1:00AM and 2:00AM regardless of events. If there is a problem with transmission the device will alert the physician within 24 hours and this will help to maintain compliance of transmission.

If no events occur the device will be interrogated prior to explantation at the end of the 6 month monitoring period.

The study investigators will be responsible for telemetry review. The patient's treating cardiologist will be notified of events of clinical significance. Treatment of the arrhythmias will be based on current clinical guideline recommendations for bradycardia and VA. Clinical follow up will occur via standard of care clinical visits.

SCD is defined as sudden and unexpected death within 1 hour of cardiac symptoms in the absence of progressive cardiac deterioration, unexpected death during sleep, or unexpected death within 24 hours after last being seen alive. Study participants who experience SCD while monitored and are successfully resuscitated after life-threatening VA will receive an implantable cardioverter defibrillator based on current clinical guidelines. These and other arrhythmic events recorded by the implantable monitor, or SCD that cannot be successfully resuscitated, will be considered events of interest and NOT adverse events, as these are not a consequence of monitoring via the implantable device.

At the end of the 6 month monitoring period, the device will be explanted. Participants will be offered the choice to retain the device until battery end of life if clinically indicated. However, patients who opt to continue monitoring will be informed that their insurance

company will be billed for clinically indicated monitoring and explantation outside the study time frame.

For any patients who expire during the study monitoring period, the terminal rhythm of participants who die will be reviewed remotely via the Biotronik website irrespective of whether the monitor can be retrieved. Patients will be informed of this possibility during the consent process.

For stage III patients with existing ICD or pacemakers, rhythm monitoring will be obtained from the device over a 6 month timeframe and may be retrospective if applicable.

Patients with existing implantable cardiac devices will undergo a device interrogation at enrollment and at the end of the 6 month monitoring period. If available, records from interim routine and unscheduled clinical device interrogations during the 6 month monitoring period be requested for review by the investigators.

Routine clinical follow up will be continued including clinically indicated ECHOs,ECGs, and blood work.

Timeline for testing:

Tests	
ECHO- TTE	At baseline (clinical echo within 6 months of enrollment date) and scheduled as clinically indicated
Biopsy or technetium pyrophosphate scintigraphy	As clinically indicated, inclusion criteria for the study
EKG	Clinically indicated at baseline (within 6 months of enrollment) and when clinically indicated
MRI with T1	When clinically indicated
Cardiopulmonary exercise test	When clinically indicated
Biomonitor 3	Monitored with a clinically significant event
NT proBNP	When clinically indicated, inclusion criteria for the study based on clinically indicated testing
Troponin T	When clinically indicated, inclusion criteria for the study based on clinically indicated testing
Labs: CBC, Basic Metabolic Panel, Mg	When clinically indicated
Urine pregnancy	At baseline for women of child bearing potential

An insertable monitor may be removed emergently at the investigator's discretion at any time subsequent to an implant procedure. Reasons for removal include, but are not limited to: patient death; loss of sensing; inability to program/interrogate the inserted monitor; infection, EOS (normal or premature); or other reason(s). Complications related to other portions of the insertable monitor system may also result in insertable monitor removal.

6 Statistical Plan

6.1 Sample Size Determination

This study is a pilot study, to assess the true arrhythmic burden seen in the TTR-wt population. This is a novel study design and no research exists. This study will provide the basis for future, larger scale trials.

6.2 Statistical Methods

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the two groups. These analyses will help identify baseline clinical characteristics that may be associated with risk of sudden cardiac arrest or bradycardia requiring pacemaker implantation.

Handling of Missing Data

This is a prospective pilot study and all patients will be treated and monitored at Mayo Clinic in Rochester, MN. All clinically relevant data will stored in the Mayo Clinic electronic medical record (Epic). Data queries will be performed at the conclusion of the study to recover any missing data.

Primary Hypothesis:

The primary hypothesis that arrhythmogenesis and SCD risk in this population is influenced by amyloid cardiomyopathy stage rather than reduced left ventricular ejection fraction, which is often a marker of late disease and increased mortality due to heart failure, and that SCD due to asystole, rather than VA which could be treated with ICD. Conduction system disease causing heart block, atrial arrhythmias and VA leading to SCD may occur earlier in the disease process and treatment of AF, VA, and heart block could improve both morbidity and mortality.

A Student's t-test will be used to compare differences in arrhythmia burden between the patients in the two groups (early stage I-II vs stage III either with any implanted cardiac device).

6.3 Subject Population(s) for Analysis

All-implanted population: Any subject enrolled into the study and had a device implanted.

7 Safety and Adverse Events

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the appropriate regulatory committees per their requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events for the Biomonitor 3 will not be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.4.2 Anticipated Risks.

We will gather information from the subject as soon after the occurrence as possible to decrease recall bias or omission. Use of a combination of both closed-ended questions as

well as open-ended responses may provide better information rather than only one or the other.

The investigator and team will use lay language in the informed consent process to assure reliable information is being captured. Additionally subjects will be instructed to contact the investigator or study coordinator if the subject feels that they may possibly have experienced any adverse events between scheduled study visits or contacts.

In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs. FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful AE information. The ultimate goal is to provide more meaningful information to IRBs, particularly when sponsor analysis (including an analysis of the significance of the adverse event, with a discussion of previous similar events where appropriate) is made available to IRBs.

7.1 Definitions

The only definition of an adverse event in the device regulations (21 CFR 812) is for an "Unanticipated Adverse Device Effect." The regulations reference "Adverse Effects" and "Adverse Device Effects" may be either anticipated or unanticipated. Investigators will maintain records of all relevant observations including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, implantation of the device, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Effect (Event)
Any infection at the site of the implantable device, excessive unstoppable bleeding or development of a hematoma requiring evacuation, or malfunction of the FDA approved device in a subject involved in this clinical trial. Malfunction of the device includes but is not limited loss of sensing; inability to program/interrogate the inserted monitor; or premature EOS. Complications related to other portions of the insertable monitor system may also result in insertable monitor removal.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator is aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Preexisting Condition
A preexisting condition is one that is present at the start of the study.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event Reporting Period

1. Patients will be monitored for 6 months and all adverse events withing the 6 month time frame will be recorded. If patients choose to retain the monitor, all subsequent monitoring will be clinically indicated.

7.2 Recording of Adverse Events

Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal physical exam of the implant site will be recorded in the source document.

All adverse events occurring during the study period will be recorded. All observed or volunteered adverse effects (serious or non-serious) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the device. The clinical course of each event will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause.

The only laboratory values that will prompt an investigation would be an elevated leukocytosis IN ADDITION to a physical inspection of the implanted site. If the implanted site is erythematous, hot, swollen, or there is drainage from the skin would further steps need to be taken to possibly extract the device. Positive blood cultures would indicate the necessity of a physical exam and inspection of the implant site.

A form will be created for capturing information related to adverse events and submitted to the IRB.
Adverse Event CRF:

- Subject Study Number/Identifier
- Device information (model and serial number)
- Date of event onset
- Description of the event
- Indicate if device needed to be explanted
- Subject current status, or if the event was resolved
- Principal Investigator assessment of if the event was serious and justification for

determination

- Principal Investigator assessment of causality and relationship to study treatment.

7.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within 10 working days and Mayo IRB within 5 working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

7.3.1 Sponsor-Investigator Reporting, Notifying Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Deviations from the investigational plan.

The sponsor-investigator shall notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

7.4 Stopping Rules

The study involves implantation of an FDA approved monitoring device to monitor arrhythmias and does not provide any treatment. If frequent adverse events occur with implantation of the monitoring device that require early explantation (i.e. frequent infection), the study will be stopped.

7.5 Medical Monitoring

The sponsor-investigator will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 12) In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Our source documents include original documents, and data records including hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

All data will be stored in the Mayo Clinic electronic medical record, and any data relevant to the study will be entered into the study database stored on secure Mayo Clinic servers which is compliant with the FDA's electronic records and electronic signatures regulations at 21 CFR Part 11.

8.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space

on the CRF is left blank because the procedure was not done or the question was not asked, it will be recorded as "N/D". If the item is not applicable to the individual case, write "N/A". CRFs are electronic and are incorporated into the

Data Management

The data will be stored and managed as per protocol at the Mayo Clinic.

Data Processing

This is a single center study. All data will be entered monthly for all patients without arrhythmias and data will be entered within a week of a clinically relevant arrhythmic occurrence.

Data Security and Confidentiality

This is a single site study. The Mayo Clinic, Rochester, MN campus, is a major referral center for amyloidosis. Data security is of utmost concern at Mayo Clinic and data security and confidentiality will be maintained in accordance of Mayo Clinic standards.

Data Quality Assurance

Data will be entered into a RedCap secure database by the same person entering data on the CRFs. This data will be reviewed by one additional person on the protocol.

Data Clarification Process

Any questions about data will be address by the study coordinator or the person entering data.

8.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717,

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Data and safety monitoring provides a clinical investigation with a system for appropriate oversight and attention to the protection of human subjects by the investigator, research team, or an independent reviewer. A Data and Safety Monitoring Plan is a quality assurance plan for a research study. A written Data and Safety Monitoring Plan (DSMP) has been created.

Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

9.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11 Study Finances

11.1 Funding Source

The study is financed through Pfizer, Mayo Clinic and Biotronik.

12 Publication Plan

Study results will be published on completion of the study.

13 References

http://circ.ahajournals.org/content/136/Suppl_1/A16347

1. Falk R, Dubrey SW. Amyloid Heart Disease. Progress in Cardiovascular Disease 2010;52:347-361.
2. Gertz MA, Benson MD, Dyck PJ et al. Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis. J Am Coll Cardiol 2015;66:2451-2466.
3. Maurer MS, Hanna M, Grogan M et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). J Am Coll Cardiol 2016;68:161-72.
4. Barbhaiya CR, Kumar S, Baldinger SH et al. Electrophysiologic Assessment of Conduction Abnormalities and Atrial Arrhythmias Associated with Amyloid Cardiomyopathy. Heart Rhythm 2016;13:383-390.
5. Tan NY, Mohsin Y, Hodge DO et al. Catheter Ablation for Atrial Arrhythmias in Patients with Cardiac Amyloidosis. Journal of Cardiovascular Electrophysiology 2016;27:167-1173.
6. Hess EP, White RD. Out-of-hospital cardiac arrest in patients with cardiac amyloidosis: presenting rhythms, managment and outcomes in four patients. Resuscitation 2004;60:105-111.
7. Lin G, Dispenzieri A, Kyle R, Grogran M, Brady PA. Implantable Cardioverter Defibrillators in Patients with Cardiac Amyloidosis. Journal of Cardiovascular Electrophysiology 2013;24:793-798.
8. Sayed RH, Rogers D, Khan F et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. European Heart Journal 2015;36:1098-1105.
9. Lin G, Dispenzieri A, Brady PA. Successful termination of a ventricular arrhythmia by implantable cardioverter defibrillator therapy in a patient with cardiac amyloidosis: insight into mechanisms of sudden death. Eur Heart J 2010;31:1538.
10. Gillmore JD, Maurer MS, Falk RH et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016;133:2404-12.
11. Hosch W, Kristen AV, Libicher M et al. Late enhancement in cardiac amyloidosis: correlation of MRI enhancement pattern with histopathological findings. Amyloid 2008;15:196-204.
12. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585-94.
13. Castano A, Narotsky DL, Hamid N et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879-2887.
14. Damy T, Costes B, Hagege AA et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J 2016;37:1826-34.
15. Adams D, Gonzalez-Duarte A, O'Riordan WD et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med 2018;379:11-21.

16. Benson MD, Waddington-Cruz M, Berk JL et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med 2018;379:22-31.
17. Maurer MS, Schwartz JH, Gundapaneni B et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med 2018.
18. Rezk T, Whelan CJ, Lachmann HJ et al. Role of implantable intracardiac defibrillators in patients with cardiac immunoglobulin light chain amyloidosis. British Journal of Haematology 2017.
19. Kober L, Thune JJ, Nielsen JC et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. The New England Journal of Medicine 2016;375:1221-1230.
20. Vaduganathan M, Patel RB, Michel A et al. Mode of Death in Heart Failure with Presered Ejection Fraction. Journal of American College of Cardiology 2017;69:556-569.
21. Grogan M, Dispenzieri A. Natural History and therapy of AL cardiac amyloidosis. Heart Failure Review 2015;20:155-162.
22. Hamon D, Algalarrondo V, Gandjbakhch E et al. Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis. International Journal of Cardiology 2016;222:562-568.
23. Varr BC, Zarafshar S, Coakley T et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. Heart Rhythm 2014;11:158-162.
24. Castano A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging diseae-modifying therapies from organ transplantation to stabilizer and silencer drugs. Heart Failure Review 2015;20:163-178.