AngelMed Guardian® System
for the Alerting of Patients to ST Segment Changes Indicative of Coronary Artery Occlusion

PMA P150009

SPONSOR EXECUTIVE SUMMARY

CIRCULATORY SYSTEM DEVICES PANEL

MEETING DATE: March 16, 2016

Sponsored by Angel Medical Systems, Inc.

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Definition of Terms

ACS	Acute coronary syndrome
AE	Adverse event
AGEA	AngelMed Group for Endpoint Adjudication
AHA	American Heart Association
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
AQOL	ALERTS quality-of-life
BBB	Bundle branch block
CABG	Coronary artery bypass grafting
CI	Confidence interval
CK	Creatinine kinase
CPA	Confirmed positive alarm
CrI	Credible interval
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
EXD	External alerting device
FDA	Food and Drug Administration
HF	Heart failure
GEE	Generalized estimating equation
ICD	Implantable cardioverter defibrillator
IDE	Investigational device exemption
IEC	International Electrotechnical Commission
IMD	Implantable medical device
IVUS	Intravascular ultrasound
LED	Light-emitting diode
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NCPA	Non-confirmed positive alarm
NSTEMI	Non ST-segment elevation myocardial infarction

List of Abbreviations and Definition of Terms

PCI	Percutaneous coronary intervention
PMA	Premarket approval
PPV	Positive predictive value
QOL	Quality of Life
RV	Right ventricle
SAP	Statistical analysis plan
SD	Standard deviation
STEMI	ST segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1 SYNOPSIS

The AngelMed Guardian® System is a first-in-class, implantable cardiac monitor designed to alert patients to ST segment changes indicative of acute coronary occlusions, the primary cause of heart attacks (myocardial infarctions [MI]). The Guardian System is designed to reduce the time from a coronary occlusion until presentation at a medical facility.

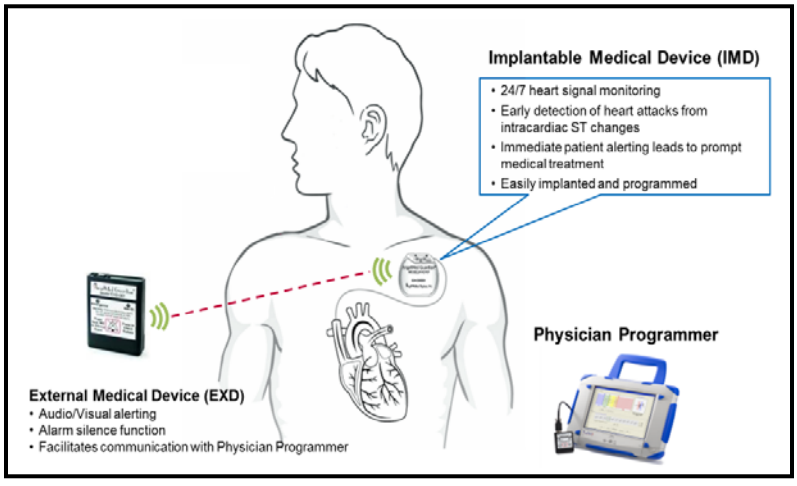
AngelMed is proposing the following indication for use of the Guardian System:

> *The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion. Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.*

The Guardian System includes three components (Figure 1):

- The implantable medical device (IMD) continuously monitors the patient's heart through a standard pacemaker lead at the RV apex. Significant acute ST segment changes from the patient's baseline trigger an Emergency Alarm; the patient is alerted by a vibrational alert within the IMD. The implant procedure for the IMD is identical to the procedure to implant a single-chamber pacemaker.
- The external device (EXD) provides redundant visual and acoustic alerting.
- The physician programmer retrieves data captured by the IMD and is used to program patient-specific ST change detection thresholds.

Figure 1: AngelMed Guardian System



The rationale for the development of the Guardian System was to address the unmet need for earlier treatment of heart attacks and other acute coronary syndromes in high-risk patients:

- ***Earlier treatment, better outcomes ("time is muscle").*** Reducing the delay from occlusion of a coronary artery to reperfusion has become a universally accepted strategy in cardiology as a means to decrease heart muscle damage. This well-accepted fact led to initiatives by professional societies that have successfully reduced door-to-balloon times in

emergency departments in the United States, and throughout the world. Today, the largest barrier to timely treatment of MI remains patient delay. Symptom-to-door times have not improved despite patient educational efforts emphasizing the importance of recognizing and responding to symptoms of a heart attack.

- ***Reliance on symptoms for prompting treatment for coronary occlusions is inadequate.*** The clinical standard of care in the United States for the treatment of heart attacks requires that a patient has heart attack symptoms, recognizes them, and then takes prompt action. Unfortunately, many patients wait to see whether their symptoms subside before seeking medical attention, exacerbating damage to the heart and increasing the likelihood of cardiac death. Even more importantly, one third of heart attacks occur without recognized symptoms. Patients who suffer silent MI have nothing to prompt them to seek medical attention.
- **The only solution to reduce time-to-door is continuous intracardiac ST monitoring of the heart and alerting patients to take action**. The current gold standard for electrographic detection of acute coronary occlusion is significant ST segment change in the absence of elevated heart rate. Total coronary artery occlusion without collaterals generates highly-specific, rapid, and progressive ST segment changes that begin within seconds of a coronary occlusion. An implantable continuous ST monitor with alerting features like the Guardian System is the only way to overcome the "wait-and-see" mindset of patients who suffer a heart attack with symptoms, and to provide a prompt for patients who have heart attacks without symptoms.

The safety and efficacy of the Guardian System was evaluated in the pivotal ALERTS randomized clinical trial. In total, 907 patients were implanted with a Guardian System and randomized 1:1 to the Treatment or Control groups. All patients received the Guardian implant. The detection and alerting features of the Guardian System were activated in the Treatment group, while only the detection feature was activated in the Control group. Occlusion-to-door times were assessed in both groups by retrieval of the data from the Guardian after there was a "confirmed" coronary occlusive event with positive tests following patient presentation, as adjudicated by an independent committee.

ALERTS is the first study that has been able to measure the time from the onset of a coronary occlusion, as detected by rapid and substantial ST segment changes, to arrival at a medical facility. Similarly, as the first continuous intracardiac monitor, ALERTS is also the first study that has been able to evaluate the behavior of patients who experience asymptomatic occlusive events.

The *primary safety objective* of the ALERTS Study was to demonstrate that the rate of freedom from system-related complications among patients implanted with a Guardian System was greater than 90% at 6 months. The trial met its primary safety objective with a 96.7% freedom from system-related complications. System-related complications occurred with an incidence similar to those observed historically in studies of single-chamber pacemakers.

The *primary efficacy objective* of the ALERTS Study was to demonstrate that the rate of a composite primary endpoint was lower in the Treatment group in the first 6-months after device implant and randomization. This composite consisted of:

- late arrival at a medical facility (>2 hours from Guardian detection) for a confirmed event,
- new pathological Q-waves (assessed by a blinded ECG core lab), and/or
- cardiac or unexplained death

The trial did not meet its primary efficacy endpoint. As a first-in-class device, several limitations of the study design that were not anticipated at the time the trial was initiated negatively impacted the primary efficacy endpoint. These are discussed in more detail in Section 4.7. Despite the failure to meet the primary efficacy endpoint, there are a number of clinically meaningful and statistically significant findings in the ALERTS Study, which include:

- The study met two of its secondary endpoints reflecting its designed purpose of prompting patients to seek medical attention quickly after confirmed occlusive events:
    - Treatment patients achieved significantly shorter occlusion-to-door times than Control patients. The median time from the *first* Guardian detection of an occlusion to arrival at a medical facility was **51 minutes** for the Treatment group compared to **22 days** in the Control group.
    - The rate of late arrival (>2 hours) after the onset of a coronary occlusion was lower in the Treatment than the Control group. In terms of the clinical goal of *early* arrival (≤2 hours), **85%** of confirmed occlusive events in the Treatment group had an arrival time to a medical facility within 2 hours, compared to just **6%** of confirmed occlusive events in the Control group.
- Supportive "event-based" analyses of the primary efficacy endpoint
- High patient acceptance, with 93% of patients requested re-implant after end of battery life.
- Significant improvements in quality of life after alerting was enabled in a sub-study.

Overall, AngelMed believes that the totality of the data support the safety, efficacy, and positive benefit-risk profile of the Guardian System for the proposed indication for use.

- ***Safety:*** The safety risks of Guardian System are limited to those of a single-chamber pacemaker, which have been well studied over the last 50 years.
- ***Efficacy:*** Patients in the ALERTS study who had Guardian System alerts activated had considerably earlier presentations for confirmed coronary occlusive events than Control patients who did not have the benefit of alerting.
- ***Benefit-Risk:*** Given the large unmet need for earlier presentation of patients with heart attacks, the demonstrated benefit of Guardian alerts for earlier presentation for confirmed coronary occlusive events, and the well-understood safety profile of the device, the AngelMed Guardian System has a positive benefit-to-risk profile for its proposed indication.

The ALERTS Study was designed to evaluate the safety of the implant and effectiveness of the Guardian System in reducing the time-to-door for occlusive events. AngelMed's controlled post-marketing study will be powered to evaluate the full capability and clinical benefits of the Guardian System.

2 UNMET NEED FOR EARLIER TREATMENT OF HEART ATTACKS

Summary

- In the United States, there are an estimated 735,000 heart attacks per year; of these, 210,000 are recurrent heart attacks.
- The rates of morbidity and mortality are higher for recurrent heart attacks than first heart attacks.
- Delays in treatment for heart attacks lead to worse clinical outcomes for patients, including diminished ejection fraction and higher mortality.
- Recognized symptoms such as chest pain provide the only current standard of care prompt for patients to take action for a heart attack to avoid such delays. However, chest pain is not a sensitive, specific, or timely prompt:
  - **Not sensitive:** approximately 1/3 of heart attacks are silent
  - **Not specific:** the positive predictive value of chest pain for AMI and ACS events is only approximately 15-20%
  - **Not timely**: most patients who recognize their symptoms take many hours after symptom onset before they present at a medical facility, and delays of days or weeks have been reported between the first onset of symptoms and presentation for MI.
- Coronary occlusions without collaterals to viable myocardium create rapid, acute ST segment changes, typically within 30 seconds. This makes the continuous monitoring of ST segment changes a viable way to monitor for heart attacks.
- Currently available technologies including Holter monitors and implantable loop recorders cannot measure ST segment changes.
- An implantable continuous ST segment monitoring technology with real-time alarm capability, is the only viable solution to address the unmet need for earlier treatment of heart attacks.

2.1 Epidemiology of Recurrent Heart Attacks

In 2015, the American Heart Association (AHA) reported that there are an estimated 735,000 heart attacks (i.e., acute myocardial infarction [AMI]) in the United States every year.[1] Of these, 525,000 are first-time heart attacks and 210,000 are recurrent heart attacks among heart attack survivors.

The morbidity and mortality of first heart attacks are serious, though recurrent events carry even greater risks of death and heart failure.[2] In the VALIANT cohort, 38.3% of patients who suffered a recurrent MI died within one year compared to the one-year mortality rate of 10.3% for the entire cohort (adjusted HR 2.4, 95% CI 1.7 – 3.2). The magnitude of the effect was similar for the composite outcome of death and heart failure (adjusted HR 2.3, 95% CI 1.7 – 3.1).[2]

2.2 Impact of Treatment Delay on Clinical Outcomes

There is universal consensus in the medical community that reducing the time to treatment for heart attacks is beneficial to patient outcomes.[3] Once a patient arrives at a medical facility, the goal of reperfusion treatment for an AMI is a door-to-balloon time of 90 minutes or less.[4] This objective appears to have been achieved by the majority of U.S. institutions that treat AMI based on quality metrics captured by the Centers for Medicare & Medicaid Services (CMS).

Despite these improvements in door-to-balloon time, in-hospital mortality has not changed for patients treated for AMI. This has been attributed largely to the patient delays in seeking care when coronary occlusions, with or without symptoms, first occur.[5,6] Delays from the onset of MI symptoms to the arrival at a medical facility (i.e., symptom-to-door times) have been studied extensively.[3,7-11] The median symptom-to-door times for MI with recognized symptoms have ranged in the literature from approximately 2 to 6 hours; and, symptom-to-door times do not improve following a first MI.[12]

The increased morbidity and mortality due to treatment delays include the associated increased risk of heart failure and arrhythmias, higher rates of hospitalization, sudden cardiac death, and a significant reduction in quality of life.[13,14] The primary diagnosis of heart failure, in particular, from such cardiac damage is also extremely costly, with recent estimates suggesting the cost is as high as 3.2% to 5.8% of the total medical costs in the United States.[15]

The impact of delay in treatment times has been well established in the literature. A longitudinal study of 1791 patients with MI treated by primary angioplasty,[3] found that every 30-minute delay in time from symptom onset to treatment resulted in:

- 7.5% increase in the relative risk for mortality at one year, and
- 8.7% increase in the relative risk for a low ejection fraction leading to heart failure

2.3 Inadequacy of Reliance on Symptoms to Prompt Treatment for Heart Attacks

The current standard of care places all of the emphasis on the patient performing multiple steps correctly in order to achieve a positive outcome. The current paradigm requires patients to:

- Have symptoms; then,
- Correctly recognize those symptoms as a heart attack; and then,
- Act promptly to seek medical attention.

The barriers to each of the steps above are substantial. Many patients with heart attacks experience no symptoms whatsoever or have symptoms that they do not recognize. Reports on the National Registry of Myocardial Infarction found that 33% of patients with confirmed heart attacks did not report chest pain on presentation to the hospital.[16] For older patients, women, and diabetics, the rate of silent MI increases further.[17,18]

The specificity of chest pain is low and is a poor predictor of AMI. A study by Bright and Pocock,[17] the investigators reported that only 203 out of 1305 patients transported to the hospital

with chest pain had a diagnosis of AMI in the emergency department, a positive predictive value (PPV) of only 15.6%. In another study, chest pain provided a combined 12.9% PPV for AMI or ACS, where 893 patients were assessed and only 34 (3.8%) were diagnosed with AMI and 81 (9.1%) with ACS.[19]

Chest pain does not produce timely action by heart attack victims. Studies have found that, for true positive AMI events, approximately 55% of patients arrive at a medical facility more than 2 hours after symptom onset,[20] with other studies showing even longer delays. Importantly, public education has not been effective in reducing symptom-to-door time.

Overall, there is an overwhelming consensus in the medical community that earlier treatment of heart attacks is highly beneficial for patient outcomes. Unfortunately, the response times for heart attacks that occur with symptoms are often delayed by a variety of factors (e.g., patients wait to see if their symptoms to subside, atypical symptoms that go unrecognized) and do not appear to improve with education or even having had a prior MI. There are currently no prompts for patients who suffer a heart attack in the absence of recognized symptoms.

2.4 Rationale for Continuous ST Segment Monitoring to Identify Coronary Occlusion

The current gold standard for recognition of heart attacks is significant changes in the ST segment on a 12-lead ECG in the absence of elevated heart rate. Although fixed coronary artery narrowing may result in ST segment depression with elevated heart rates, rapidly progressive ST segment changes within the normal heart rate range is highly specific, and nearly always related to complete thrombotic or vasospastic coronary artery occlusion. Such ST segment changes often precede and are the result of early repolarization of ischemic heart muscle in the portion of the heart whose blood supply has been cut off.

The classification of ST-elevation MI (STEMI) versus non-ST-elevation MI (NSTEMI) is based on the 12-lead ECG reading taken as a snapshot at the single point in time when the patient presents at a medical facility, usually hours after the onset of occlusion. Significant intracardiac and surface ECG ST segment changes have been shown to be present within a minute of coronary occlusion.[21,22] If a surface ECG were in place at the time of coronary occlusion, most heart attacks would likely be classified as STEMIs. The majority of MIs present as NSTEMI either (1) because thrombotic occlusions often open and close during the progression of a heart attack following plaque rupture, or (2) hours after an occlusion, ST segment changes are no longer present due to the damage to the downstream heart muscle.[21]

Continuous monitoring of a patient's ST segment could allow one to rapidly detect ST segment changes at the onset of occlusion. If patients were then alerted, evaluation and appropriate intervention could occur soon enough to prevent significant heart muscle damage. Early intervention, such as taking an aspirin early in the progression of the thrombus, could also be effective when the clot is primarily platelet based.

Detecting these ST changes when they happen requires a continuous ST monitor. Unfortunately no existing technology can provide this function. Specifically:

- Current surface technologies (e.g., Holter monitors) cannot be worn for long periods of time, lack a patient self-normalized algorithm that can detect ST changes, and are prone to noise, axial shifts of the heart, and patient-compliance issues.
- A single short vector (e.g., with an implanted loop recorder) is insufficient to detect occlusions of all three coronary arteries.

An implantable device with a pacemaker lead at the apex of the right ventricle (RV) and a detection algorithm designed to detect ST changes indicative of acute coronary occlusion would provide a reliable continuous monitor that could accurately detect occlusion of any of the three major coronary arteries. The reasons for the appropriateness and need for such a technology include the following:

- Intracardiac electrograms from a pacemaker lead implanted at the RV apex are well suited for ST segment monitoring as they are extremely stable, have high signal-to-noise, and are immune to axial shifts of the heart from patient motion.
- The RV apex is the junction point for ventricular tissue and therefore is the ideal place to monitor ST segment changes because occlusions in all three major coronary arteries are reliably detected.[21,23,24]
- The potential for ST segment changes to occur slowly from coronary narrowing and other ailments like pericarditis require a detection algorithm to be patient-referenced and to look for acute changes rather than absolute ST levels.

The only technically feasible solution to the unmet need for earlier treatment of heart attacks is an implanted continuous ST segment monitor like the Guardian System, which can identify acute coronary occlusions when they occur and prompt patient action independent of the patient having recognized symptoms. Such a monitor and alerting system eliminates the patient decision delay associated with recognized symptoms and, even more importantly, provides a prompt for patients with no symptoms or atypical symptoms.

3 ANGELMED GUARDIAN SYSTEM

Summary

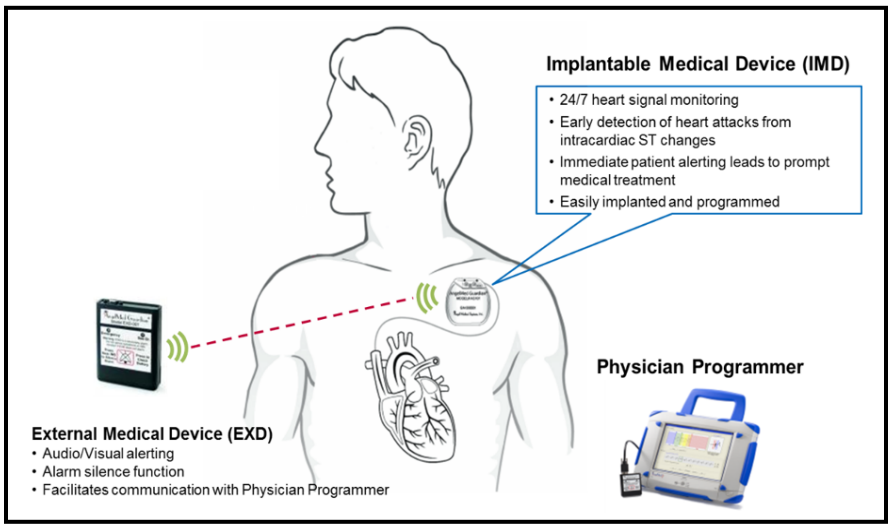
- The Guardian System is comprised of an implantable device (IMD) connected to a standard pacemaker lead, an external alerting device (EXD), and a physician programmer used to program and interrogate the IMD.
- Every 90 seconds, the IMD records 10 seconds of electrogram data and references it against each patient's self-normalized baseline, which is based on the last 24 hours of electrogram data.
- ST segments are extremely stable from one day to the next, except when a coronary becomes totally occluded. Thresholds for ST shift detection are self-referenced from 14 days of recordings (approximately 10,000 heartbeats).
- Significant acute ST segment changes from baseline at a non-elevated heart rate, indicative of coronary occlusion, trigger an Emergency Alarm. Conditions that could interfere with ST segment monitoring trigger a See Doctor Alert.
- Extensive human-factors testing was conducted with guidance from the FDA to ensure that patients could properly recognize alarms, remember what action they should take, and learn to tell the difference between Emergency Alarms and See Doctor Alerts over an extended period of time.

3.1 Overview of the Guardian System

The Guardian System includes 3 components (Figure 2):

- An Implantable Medical Device (IMD) to implement a ST-shift detection algorithm and provide a vibratory alert, similar to that used in modern cell phones. The IMD is connected to a standard active fixation pacemaker lead with an IS-1 connector that is implanted with the tip into the RV apex. The implant procedure for the IMD and lead are identical to the implant of a single-chamber pacemaker.
- An External Device (EXD), providing wireless communication with the IMD at distances of up to 2 meters. The EXD serves the following functions:
    - Provides redundant patient alerting using auditory and visual alerts to augment the vibrational alert provided by the IMD; and
    - Allows the patient to acknowledge and turn off the alerting signals and the redundant reminder alerts
- A Physician Programmer designed to program the IMD and upload cardiac data recorded by the IMD.

Figure 2: AngelMed Guardian System



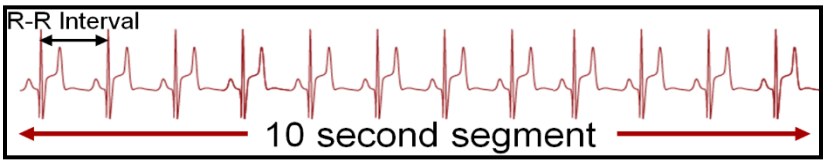
The Guardian System provides two levels of alerting, each with distinct vibratory, acoustic, and visual alerts validated by human factors testing:

- **Emergency Alarms** – signal the detection of acute ST segment changes at normal heart rates indicative of coronary occlusion
    - Alarm attributes:
        - IMD vibrates
        - EXD beeps in a synchronized 3-2-3-2 pattern, and flashes a red LED
    - Patients are trained to recognize this alarm, call 911, and seek medical attention immediately
    - Data collected by the IMD include ST levels, heart rate, and electrogram strips, which are stored in the device's internal memory for later review. The device saves data from 24 hours before the alarm to 8 hours after the alarm.
- **See Doctor Alerts** – signal a condition that is interfering with ST segment monitoring for coronary occlusion such as low, high, and irregular heart rates
    - Alert attributes:
        - IMD vibrates
        - The EXD beeps once every 7 seconds, and flashes a yellow LED
    - Patients are trained to recognize this alarm and are instructed to schedule appointment with physician in 1 to 2 days
    - Electrogram strips from 24 hours before and at the time of the alert are saved

3.2 Guardian System ST Detection Algorithm

AngelMed has developed a proprietary algorithm to detect rapid intracardiac ST segment changes that are indicative of acute coronary artery closure. Every 90 seconds, the Guardian analyzes a 10-second intracardiac electrogram (Figure 3). The average ST segment level, average PQ segment level, R-wave height, and the RR interval (i.e., instantaneous heart rate) are calculated for each electrogram sample. If rhythm or ST segment abnormalities are noted, the interval between the sampling of electrograms shortens to once every 30 seconds.

Figure 3: 10-second Electrogram Segment



The RR interval is used to classify each sample into one of the following heart rate ranges:

1. "Low" heart-rate (i.e., below the patient's normal range)
2. "Normal" range (i.e., range of resting and ambulatory heart rates)
3. "Elevated" ranges that are above the "Normal" range (as might be seen during exercise)
4. "High" heart-rate (i.e., above the elevated range)

This heart-rate range categorization allows the Guardian to distinguish normal heart rate "supply-related" ischemia associated with coronary occlusion, from "demand-related" ischemia due to coronary narrowing and elevation of heart rate.

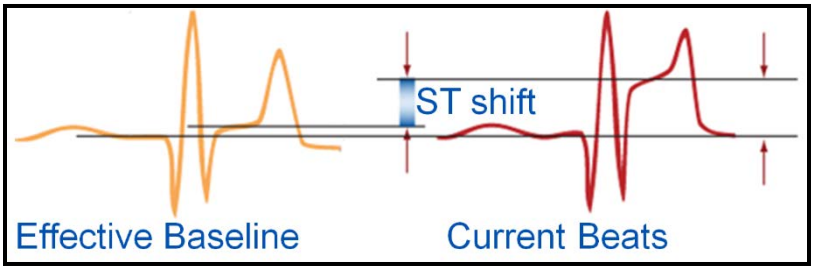
Each patient's baseline is continuously updated every hour based upon the previous 24 hours of electrogram data collected in the "Normal" heart rate range. This composite baseline is used to determine the "normal" ST segment shift range for each patient (i.e., ST segment compared to PQ segment). Each captured 10-second segment is statistically compared to this composite baseline segment. This comparison makes it possible to reliably detect an acute change from normal in the ST Segment that indicates an occlusive event has occurred. To prevent false ST segment shift determinations, premature beats are excluded from ST segment analysis.

Extended periods of abnormal heart rate (i.e., heart rates consistently in the "Low" or "High" range) or persistent irregular rhythms will trigger a See Doctor Alert. This alert is given because these conditions may interfere with the Guardian's ischemia detection accuracy. See Doctor Alerts are also provided for loss of signal (e.g., lead detachment) and for prolonged periods (i.e., >6 hours) of elevated heart rate.

For every QRS-T waveform in the electrogram sample, the ST segment deviation is compared to the patient's composite baseline in order to calculate the ST shift (Figure 4). The magnitude of ST shift is normalized as a percentage of the R-wave height, and is then compared to the patient's ST shift detection threshold (i.e., 3 standard deviations from the patient's baseline range, as determined by the Guardian programmer's *Autopick* function). Detection of an occlusive event requires 3 successive 10-second electrogram segments where each segment has

at least six out of eight beats with ST shifts that exceed the detection threshold while the heart rate is within the Normal range. The occlusive event triggering these 3 electrograms must last approximately 1.5 minutes due to the 30-second acquisition cycle that occurs for electrograms characterized as abnormal. When this occurs, the Guardian issues an Emergency Alarm.

Figure 4: Comparison of Current Beats to Effective Baseline



3.3 Human Factors Testing

In order for the Guardian to provide patient benefit, the alerting signals and protocols needed to be simple and robust, and patient instructions needed to be clear. With this in mind, AngelMed developed three modes of patient alerting: vibration from the IMD, and sound and flashing LEDs in a pager-sized EXD.[25] The triple-modality alerting (i.e., vibration, visual alerting, and sound) is important because this can serve to alert a patient in one modality even if a different modality is flooded (e.g., vibration can still be felt in a loud movie theater where the audible alarm may be missed or in an elderly person with hearing loss).

Extensive human factors testing was completed using patients aged 55 to 82 to identify and validate the triple-sensory modal alerting provided by the Guardian System. Human factors testing was used to evaluate both the patterns and intensities of the external and internal alerting. The results of these tests were used to determine the final alerting that would be appropriate for, and most effective in, the target patient population.

As suggested by the FDA, the two different alerting patterns adopted for use by the Guardian conformed to international standards (IEC 60601-1-8:2003). Based on human factors testing, the characteristics of these patterns were adjusted to maximize the ability of patients to clearly differentiate the two alerting levels from each other.[25]

These patterns were tested pre-clinically and in the Investigational Device Exemption (IDE) safety study called DETECT.

3.4 Early Human Studies of the AngelMed Guardian

Two clinical feasibility studies of the AngelMed Guardian were performed between 2005 and 2008.

- The CARDIOSAVER Study was an initial study of 20 Brazilian patients at high risk for a heart attack who were scheduled for percutaneous coronary intervention (PCI) of a coronary artery. The study demonstrated that, during balloon occlusion, large electrogram ST segment acute changes were present in the absence of significant collateral flow. When collaterals were observed, much smaller ST segment changes occurred because downstream tissue still received oxygen in spite of the balloon occlusion of the target vessel. Prior to PCI, a number of study patients also underwent an exercise stress test where ST depression during and after elevated heart rate was observed in the electrogram from demand ischemia. After PCI, patients were discharged and over the next 18 months the Guardian effectively detected and alerted four occlusive events in 2 patients with intravascular ultrasound [IVUS]-validated plaque ruptures.
- The DETECT Study was a safety IDE study in 20 enrolled patients conducted in the United States to assess the safety profile of the Guardian and to demonstrate that the Guardian *Autopick* function provided a reliable means for selecting ST shift detection thresholds. Two DETECT patients also had Emergency Alarms for IVUS-identified plaque ruptures.

Insights and positive results from both studies prompted AngelMed to design and conduct the pivotal ALERTS study. A report in the *Journal of the American College of Cardiology*,[23] which discusses the results of these two studies and shows several case examples of the Guardian's detection capabilities, is included as an Appendix to this document.

4 ALERTS STUDY DESIGN

Summary

- ALERTS was a 1020-patient randomized prospective trial to evaluate the safety and efficacy of the AngelMed Guardian System. Patients were randomized 1:1 to the Treatment or Control groups, where alerting was turned on or off, respectively, for 6 months.
- The study enrollment criteria were designed to include post ACS/AMI patients at high risk for recurrent ACS events by requiring they have diabetes, renal insufficiency or a TIMI risk score of 3 or greater.
- All primary and secondary endpoints were adjudicated by independent, expert committees.
- The primary safety endpoint was to demonstrate a >90% rate of freedom from system-related complications, a performance goal commonly used in pacemaker studies.
- The primary efficacy endpoint was a composite of late arrival (>2 hours) after a confirmed occlusive event, new Q-wave, and cardiac or unexplained death.
- Secondary efficacy endpoints included components of the primary efficacy composite, time-to-door analyzed continuously, and other endpoints for patients at high risk for silent ischemia.
- ALERTS was designed as a Bayesian adaptive trial in order to allow for sample size adjustments on the basis of the interim event rates to ensure the study was adequately powered. Due to statistical modeling issues and logistical difficulties discovered during the course of the trial, it was determined that the pre-specified adaptive model was not accurate in determining sample size.

4.1 Overview

The ALERTS randomized trial was designed to test the safety and efficacy of the AngelMed Guardian system by comparing the outcomes for patients with and without the benefit of Guardian alerts.

4.2 Inclusion/Exclusion Criteria

The ALERTS Study patient profile involved the following requirements:

- Advanced Multi-vessel Cardiac Disease
- An index ACS event (MI, unstable angina, or coronary artery bypass grafting [CABG]) within six months of patient enrollment
- At least one of three additional risk factors/co-morbidities: diabetes, TIMI risk score >3, or renal insufficiency

This high-risk patient profile was chosen so enrolled patients would derive the greatest potential benefit from alerting, as well as to provide a sufficient number of events within the study to demonstrate a significant benefit from alerting.

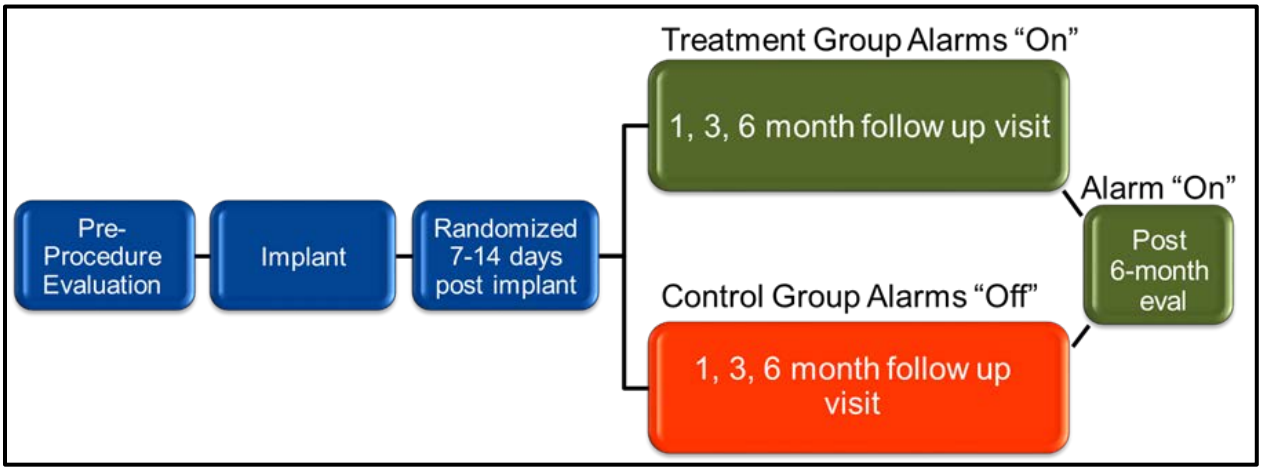
Exclusions included the presence of a pacemaker or implantable cardioverter defibrillator (ICD), low ejection fraction <35%, chronic arrhythmias (e.g. atrial fibrillation or bundle branch block) and inability to feel vibration in the left pectoral region as tested with an IMD pressed against the skin.

The full inclusion and exclusion criteria are provided in the Appendix I (Section 10).

4.3 Study Procedures

Figure 5 displays an overview of the key ALERTS Study visits and evaluations. Details for each are described in the following sections.

Figure 5: ALERTS Study Process



4.3.1 Pre-Procedural Evaluation

After enrollment, but prior to the Guardian implant, a first baseline (12-lead) ECG was recorded at the pre-procedure evaluation (i.e., pre-implant ECG).

4.3.2 Implant

The Guardian IMD was implanted in all patients who met inclusion/exclusion criteria, using a procedure identical to that of a single chamber pacemaker, requiring no additional physician education on the implant procedure itself. An FDA-approved IS-1 active fixation pacemaker lead was positioned and then fixed at or near the apex of patient's the right ventricle. Before discharge, data were retrieved from the IMD to check for proper performance and to configure the device for baseline electrogram collection.

4.3.3 Randomization

Seven to 14 days after implant, patients returned to the site to be randomized (1:1) to either the Treatment or Control groups and have their devices programmed accordingly. All patients had

ST shift detection enabled in order to assess the "time-to-door" components of primary and secondary endpoints in both groups, however only the Treatment group had alerting turned on. Randomization was stratified by site with a blocking scheme of randomly varying size blocks. A second baseline 12-lead surface ECG was also collected at the time of randomization.

Following randomization, patients in the Treatment group were provided with an EXD. Both Emergency Alarms and See Doctor alerts were triggered using the Physician's Programmer to train patients on how to recognize the alerts and silence them using the EXD. For Emergency Alarms, patients were instructed to call 911 and seek immediate medical attention. For See Doctor alerts, patients were told to call their doctor after the alert to schedule an appointment within one or two days, if possible.

Patients randomized to the Control group received the standard of care, per the treating physician and site. Both groups received the same education regarding the importance of seeking immediate medical attention if they experience the symptoms of a heart attack, regardless of whether an alert was issued by the Guardian System. Patients in both groups had identical initial programming with respect to ST segment change detection.

4.3.4 Follow-up Visits

The ALERTS protocol required all patients to have follow-up visits at 1, 3, and 6 months, then every 6 months thereafter. At each visit, the patient's IMD event status was uploaded to the Physician Programmer for review. In addition, the patient's medication records were updated. At each follow-up visit, a 12-lead ECG was also obtained, data was retrieved from the IMD, and the ischemia threshold settings were checked and adjusted, as necessary. Any adverse events or complications were also recorded. During the randomization period, the site staff and patients in the Control group were blinded to the ECG data that was transmitted to the programmer.

4.3.5 Post 6-Month Evaluation

Guardian alerts were enabled at the 6-month follow-up visit for patients in the Control group. At this time, former Control patients were trained on how to respond to Guardian alerts protocols.

4.3.6 Procedures for Emergency Alarms

In the event of an Emergency alarm, upon presentation at a study site, the time of symptom onset (if any) and the arrival time at the treatment facility were recorded. Regardless of whether chest pain was present, patients with an Emergency Alarm were to undergo a cardiac evaluation consistent with the standard of care for chest pain. This included serial cardiac enzymes, serial ECGs, recording of any adverse events, and a summary of medications taken or delivered. If deemed necessary (or if the initial standard of care tests were inconclusive or ambiguous), the protocol requested the provision of more specific standard of care tests, including stress tests and/or angiography.

Echocardiogram measurements of LVEF were not required by the protocol, but it was suggested to be collected at the pre-implant visit and at the time of discharge from any ACS event.

4.4 Event Definitions

Table 1 provides a list of terms and definitions that were used in ALERTS.

Table 1: Event Definitions in ALERTS Study

Event	Definition
Occlusive Event	A detection by the AngelMed Guardian of ST segment changes indicating acute coronary occlusion (generating an Emergency Alarm in Treatment group patients and a data capture without an alarm in Control group patients).
Positive Test	Defined as any one of the following: • ECG changes indicative of ST elevation as determined by blinded, independent Core Lab Review. **Important Note: ST depression and/or morphologic T wave changes via 12-lead ECG were also considered ECG evidence of a positive test in the eCRF materials submitted to the AGEA committee for adjudication. Unfortunately, these ECG changes (which were recorded by the ECG Core Lab in the eCRF system) were incorrectly omitted from the ALERTS Study protocol.** • Elevated enzymes/biomarkers (CK, CK-MB, or Troponin) per the standard of care at the treating hospital (e.g., above the upper limit of normal and considered within the "necrosis range" within 24 hours of the onset of ischemic discomfort) • Angiography (via independent angiographic Core Lab analysis) showing any of the following: o TIMI Flow Grade < 3 or a TIMI Frame Count > 40 o TIMI Myocardial Perfusion Grade of 0 or 1 o New thrombus, ulcer, or evidence of plaque rupture o Distal embolization o Dissection o New wall motion abnormality • A stress test (nuclear stress test preferred) that was positive for ischemia
Confirmed Event	An occlusive event confirmed by a positive test upon presentation and adjudicated by the independent AngelMed Group for Endpoint Adjudication (AGEA) committee. The "confirmed event" definition is used for all study endpoints that considered "time-to-door" or late/early arrival.
Time-to-door for a confirmed event (occlusion-to-door)	The time between an occlusive event and the time of presentation to a medical facility where there is a positive test, adjudicated by the AGEA committee, as a confirmed event. • Time from occlusion-to-door >2 hours it is considered a late arrival • Time from occlusion-to-door ≤2 hours it is considered an early arrival

Event	Definition
ACS Event	Event definition defined with FDA for evaluation of positive predictive value (PPV) of Emergency Alarms, selection of presentations where ejection fraction is measured, and evaluation of the necessity of cardiac catheterizations. In addition to core lab identified ECG and angiographic findings (as per "confirmed events"), ACS events include site-identified ECG and angiography identification of events: • A 12-lead ECG with ST Segment changes either core lab or site identified • Positive cardiac enzyme test • Angiogram by site or core lab positive for: o TIMI Flow Grade < 3 or a TIMI Frame Count > 40 o TIMI Myocardial Perfusion Grade of 0 or 1 o New thrombus, ulcer, or evidence of plaque rupture o Distal embolization o Dissection o New wall motion abnormality o >20% change in lesion when compared to baseline (disease progression) as identified by Core Lab o >50% diameter stenosis identified at site • PCI or bypass surgery was indicated by the site, in the presence of a positive internal electrogram showing ST Shift exceeding a self-normative ST Shift threshold (Guardian Alarm) • Positive stress test
Non-Confirmed Positive Event Alarm (NCPA)	An Emergency Alarm, where upon presentation at a medical facility, there is appropriate chest pain protocol testing performed but no positive test result or other indication of an ACS event was identified.
System-Related Complication	Any adverse event (AE) related to a successfully-implanted Guardian System that required an invasive procedure to correct the problem. Relatedness of an AE was determined by an independent Adverse Event Committee (AC), comprised of physicians with appropriate expertise who were external to the sponsor and who did not otherwise participate in the ALERTS study.
New Q-wave	An ECG Core lab identified new Q-wave seen in one or more ECG leads at 6 months that was not present in any baseline ECG(s) as read by the blinded ECG core lab.
Silent MI Risk Subgroup	Subgroup of patients at highest risk for an MI with no or atypical symptoms having at least one of the following characteristics: diabetes mellitus, women aged 65 years or older, or prior history of silent ischemia.

4.5 Endpoint Measurements, Adjudication, and Study Oversight

Primary and secondary efficacy endpoint measurements and adjudications were performed by a combination of independent adjudication committees and core laboratories using pre-specified charters and processes, as follows:

- **Adverse Events Committee (AC) –** independently adjudicated the primary safety endpoint data. Data was provided to this committee as requested by a representative of the study contract research organization (CRO).
- **ALERTS Group for Endpoint Adjudication (AGEA) –** identified positive clinical events for inclusion as eligible events for the time-to-door components of the primary and secondary efficacy endpoints. The sponsor only provided correlative IMD data in a blinded manner to this committee, as requested, via a representative of the study CRO organization.
- **ECG Core Laboratory at the Duke Clinical Research Institute –** performed all 12-lead ECG analyses for the ALERTS Study blinded to patient group assignment. The sponsor did not participate in the analyses of 12-lead ECGs and was blinded to the results of the adjudication of the 12-lead ECGs. The results of these analyses were used to adjudicate new Q-wave for the primary and secondary efficacy endpoints.
- **Angiographic Core Lab, PERFUSE Study Group, Harvard Medical School –** analyzed all angiograms obtained during cardiac catheterization procedures performed during the ALERTS Study blinded to patient group assignment. These evaluations were used as the gold standard certification of the occurrence of a thrombotic occlusive event, evidence of a plaque rupture, and presence of disease progression (>20% increase in coronary narrowing) for all ALERTS Study patients. The sponsor did not participate in the adjudication of angiograms and was blinded to the results from this lab.
- **Data and Safety Monitoring Board (DSMB) –** responsible for monitoring the overall conduct of the study. The DSMB met bi-annually and reviewed the data from the Adverse Events Committee and other relevant interim data in order to ensure that patient safety was being protected, to assess if the study was being properly conducted, and to determine whether the study should continue as planned or if changes (e.g., sample size) were required.

4.6 Primary Safety Objective

The primary safety objective was to demonstrate that at least 90% of patients with the Guardian System implant did not experience system-related complications by the 6-month follow-up visit.

A system-related complication was defined as any AE related to a successfully implanted system that required an invasive procedure to correct the problem, as adjudicated by the Adverse Events Committee.

4.7 Primary Efficacy Objective

The primary efficacy endpoint was to evaluate the effectiveness of the Guardian System in reducing the rate of a composite endpoint consisting of the following events:

- Late arrival at a medical facility (>2 hours from Guardian detection to door) for a confirmed coronary occlusive event
- New Q-wave (note: new pathological Q-waves identify infarctions in a new part of the heart, even if the event is not recognized by the patient)
- Cardiac or unexplained death

4.7.1 Ascertainment and Definition of Late Arrivals

The AGEA committee adjudicated all events where a patient presented to a medical facility where a positive standard of care test was obtained during the 6-month randomized period.

If the associated presentation with a positive standard of care test had a corresponding Guardian detection (occlusive event) leading up to the presentation, it was considered a "confirmed event". For each confirmed event, the amount of time that elapsed between the Guardian detection and presentation at the medical facility was considered the time-to-door (i.e., "occlusion-to-door" time) for the confirmed event. If the time from occlusion-to-door was greater than 2 hours, the event was classified as a late arrival.

Maximum Time Delay between Guardian Detection and Presentation

The initial statistical analysis plan (SAP) approved by FDA in 2008 specified a minimum time-to-door for a late arrival of 2 hours, but did not specify a *maximum* allowable late arrival time-to-door. At the first interim analysis, the study statistician queried the sponsor to define the maximum length of time that could elapse between the time of presentation with a confirmed event and the time of a preceding Guardian detection. This interval became known as the "look back window". Based on published literature as of 2012, the specification of a 7-day maximum time delay between the Guardian System detection and for late arrival was first approved by the FDA through amendment of the ALERTS SAP in May of 2012.

In 2013, while the sponsor was still blinded and prior to completion of the 6-month randomized period for a large majority of study patients, the sponsor and FDA revisited this aspect of the study protocol. The re-evaluation was prompted by new findings reported during the conduct of ALERTS, such as the Oregon Study,[26] which suggested that precursor symptoms might in fact be seen 30 days or more prior to serious cardiac events such as an MI.[26] Additional support for asymptomatic heart attacks was also identified that suggested patients with unrecognized MIs may not seek medical attention at all and that diagnosis may be delayed for months or years.[27]

These data provided a deeper understanding of the behavior of patients with silent events or events with unrecognized symptoms who might never present. In those cases, the evidence of the cardiac event only had the potential to be detected at a regularly scheduled visit. This prompted a further amendment to the ALERTS SAP approved by FDA to include additional maximum times for delay as pre-specified supplementary analyses to the primary efficacy endpoint. Therefore, in addition to the 7-day maximum, which was considered primary, additional pre-specified

windows of 10, 30, 50, 70 and 90 days were defined. FDA has agreed that the 90-day maximum delay is a reasonable way to best capture late arrivals in silent or unrecognized events because 90 days was the longest interval of time between scheduled follow-up visits in the ALERTS Study.

4.7.2 Ascertainment and Definition of New Q-Wave

The finding of a new Q-Wave at six months post randomization was made using the results obtained by the ECG Core Lab. Each 12-Lead ECG collected at pre-scheduled clinic visits was sent to the Core Lab for independent analysis. The 12-lead ECG records were de-identified so that the core lab was blinded to group membership. The presence or absence of new pathological Q-Waves (i.e., new Q-wave) at the 6-month visit was determined by comparing the baseline ECG to the 6-month ECG.

Corrections to ECG Assessment Methodology to Correct for ECG Artifacts

The underlying assumption for the pre-specified assessment of ECGs during the study was that once a new Q-wave appeared in an ECG, it would never disappear in subsequent ECGs. However, it was discovered during the conduct of the ALERTS Study, that quality control factors could cause a new pathological Q-waves to appear in the ECG at one visit and then to disappear at a later visit. These quality control issues were related to real-world issues such as inconsistent or improper electrode placement or noise in the signal.

Prior to unblinding, a serial over-read process was established by the blinded ECG Core Lab to address this quality control issue. This serial over-read process required that a new Q-wave had to meet two criteria: (1) the pathological Q-waves in the follow-up ECG could not be present in the baseline ECG at randomization; and (2) that once new Q-waves appeared, they would continue to be seen in all subsequent follow-up ECGs through six months.

This analysis used four ECGs: the single baseline ECG from the randomization visit, and the 3 ECGs from the follow-up visits at 1, 3 and 6 months. Table 2 illustrates the patterns that would qualify as a new Q-wave under this "single baseline" scheme.

Table 2: Q-Wave Patterns to Qualify for a New Q-wave with a Single Baseline

Baseline at Randomization	1 Mo. Visit	3 Mo. Visit	6 Mo. Visit
Absent	Present	Present	Present
Absent	Absent	Present	Present
Absent	Absent	Absent	Present

Post-Hoc Corrections to Address Additional ECG Artifacts

After AngelMed was unblinded and the ALERTS Study results were being analyzed, it became clear that there was further potential for an artifactual new Q-wave associated with pathological Q-waves being missed in the baseline ECG, which was conducted at randomization. As such, some patients who had pre-existing pathological Q-waves were being counted inaccurately as having had a new Q-wave.

Since the ALERTS study required pre-implant ECGs be collected for all patients, AngelMed proposed using a "dual baseline" analysis as a means to reduce artifacts and noise in order to improve the quality and accuracy of the new Q-Wave component of the primary endpoint. FDA agreed that it was a reasonable manner in which to try and re-analyze the ECG data but that use of such a "dual baseline" could only be viewed as a post-hoc analysis. While AngelMed was unblinded to top-line results of the study, the ECG core lab remained blinded to patients' randomization assignments throughout this process.

In the "dual baseline" analysis there were still only three patterns that would qualify as a new Q-wave (Table 3).

Table 3: Q-Wave Patterns to Qualify for a New Q-Wave with a Dual Baseline

Baseline Pre-Implant	Baseline at Randomization	1 Mo. Visit	3 Mo. Visit	6 Mo. Visit
Absent	Absent	Present	Present	Present
Absent	Absent	Absent	Present	Present
Absent	Absent	Absent	Absent	Present

4.7.3 Ascertainment and Definition of Cardiac or Unknown Death

The finding of cardiac or unknown death was made by the independent Adverse Events Committee using the source materials collected from each clinical site. Each patient death was classified as cardiac, non-cardiac, or unknown using the pre-specified definitions listed below:

- Cardiac death: directly related to the electrical or mechanical dysfunction of the heart
- Non-cardiac death: not classified as a cardiac death
- Unknown: insufficient information to classify a death as cardiac or non-cardiac

4.8 Secondary Efficacy Endpoints

The ALERTS study has 6 secondary endpoints. Of these, 3 were the individual components of the primary efficacy endpoints:

1. Late arrival at a medical facility (>2 hours from detection to door) for a confirmed coronary occlusive event
2. New Q-wave
3. Cardiac or unexplained death

The other 3 secondary efficacy endpoints were:

4. Time-to-door for confirmed events (i.e., "occlusion-to-door" times analyzed continuously)
5. New Q-wave among patients in the silent MI risk subgroup
6. New Q-wave or late arrival at a medical facility (>2 hours from detection to door) for a confirmed coronary occlusive event among patients in the silent MI risk subgroup

4.9 Statistical Methodology

4.9.1 Sample Size Determination

To account for uncertainty in the underlying event rate as well as the treatment effect, a Bayesian adaptive design was selected so that sample size could be dynamically determined during the course of the trial. The appropriateness of the sample size was to be evaluated at different time points during the trial, with Bayesian prediction of data values for patients who had not yet reached their six-month follow-up visit. In order to determine whether to stop or to continue patient accrual, several planned analyses were specified.

The first planned analysis occurred after 600 patients were enrolled and randomized, with subsequent analyses planned at every 300 randomizations thereafter to a maximum of 3,000 patients. As previously described in Section 4.7.2, ECG artifacts present at earlier visits impacted the interpretation of 6-month assessment of new Q-wave and, consequently, the predictive ability of the model to re-estimate sample size. As a result, the independent study statistician informed AngelMed that the predictive model could not reliably re-evaluate the sample size for the ALERTS Study.

Therefore, AngelMed made an administrative decision to cease enrollment at 1020 subjects. The curtailment of enrollment was done in a blinded manner. The only information provided to AngelMed prior to ceasing enrollment was that the predictive model suggested that enrollment continue.

4.9.2 Statistical Models for Analysis of Primary and Secondary Endpoints

All efficacy endpoints assessing the proportion of patients in each group were evaluated using beta-binomial models with non-informative prior distributions so that the data alone, and not the prior distribution, determined the significance of the results. Continuous endpoints (e.g., time from occlusion-to-door) were analyzed using the Bayesian analog of the Wilcoxon Rank Sum test with non-informative prior distributions.

4.9.3 Thresholds for Statistical Significance

Pre-specified thresholds of posterior probabilities were specified in order to determine statistical significance. Posterior probabilities are based on calculations assessing the superiority of the device to the control (or to a performance goal). A high posterior probability in a Bayesian framework is analogous to a small p-value (e.g. $p<0.05$) in a Frequentist framework:

- Primary safety endpoint significance threshold: 0.954
- Primary efficacy endpoint significance threshold: 0.983 (a higher threshold was set to control the Type-I error rate given the planned interim looks)
- Secondary efficacy endpoint significance thresholds: 0.975 (with multiplicity adjustments using the Bayesian analog to Holm's sequential step-down method)
- Significance thresholds for all other analyses were set at 0.975

4.10 Additional Analyses Supporting the Effectiveness of the Guardian

In planning a trial for a new technology like the Guardian, it is difficult to identify *a priori* the ideal endpoints to show efficacy given unknowns about the data collection mechanics. As a result, there has been considerable discussion with the FDA on additional analyses to further evaluate the totality of data. These have included:

- Additional analyses of the primary and secondary efficacy endpoints that addressed the quality control issues with ECG artifacts identified after unblinding (i.e., incorporating the "dual baseline" to maximize the accuracy of new Q-wave detection [see Section 4.7.2 for details]).
- FDA-requested event-based analyses of the primary efficacy endpoint to assess consistency with the primary endpoint analysis, which was patient-based

5 ALERTS STUDY RESULTS

Summary

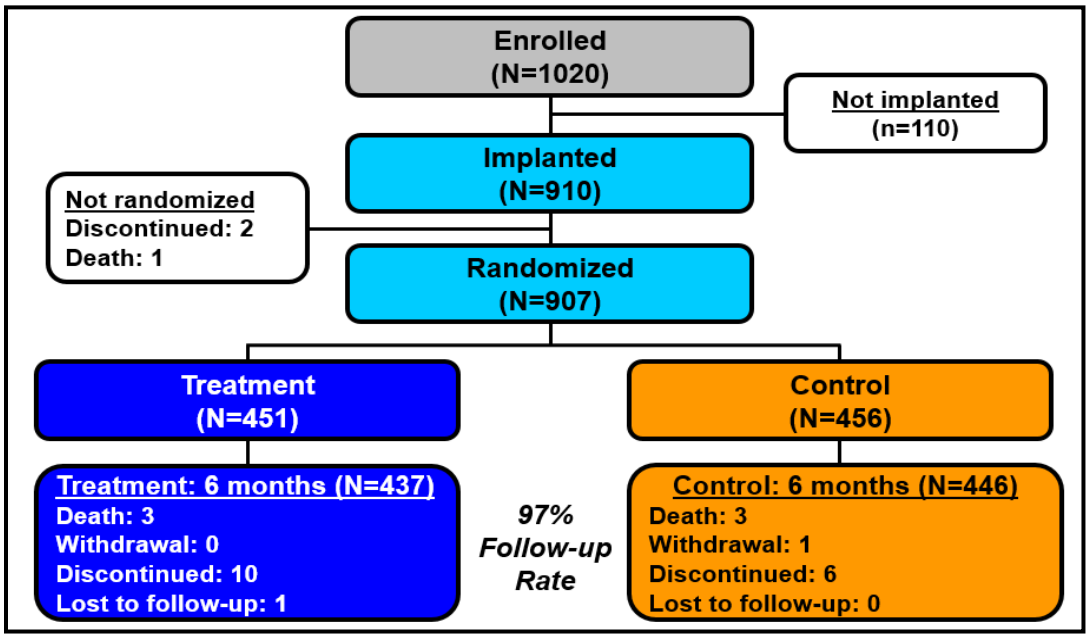
- 1020 high-risk patients were enrolled, 910 were implanted, and 907 were randomized in the ALERTS Study. The follow-up rate at 6 months was 97%.
- The primary safety endpoint of >90% freedom from system related complications was met with a 96.7% event-free rate (posterior probability >0.9999).
- The primary efficacy objective of the study was not met:
  - *Primary analysis:* Using the 7-day maximum for late arrivals, the posterior probability of superiority was 0.7856 (rate of primary endpoint events, 3.8% Treatment vs. 4.9% Control).
  - *Additional pre-specified analysis:* Using the 90-day maximum for late arrivals, the posterior probability of superiority increased to 0.9740 (rate of primary endpoint events, 3.8% Treatment vs. 6.8% Control), due to late presentations in the Control group that were not captured when using the 7-day maximum.
- The secondary efficacy endpoint assessing occlusion-to-door for confirmed events demonstrated a median time of 51 minutes in the Treatment group (for both 7- and 90-day maximum for late arrivals). In the Control group, the median occlusion-to-door time was 22 days for the 90-day maximum and 30.1 hours for the 7-day maximum. The posterior probability of superiority was >0.9999 for both analyses.
- The secondary endpoint for the rate of late arrival (>2 hour after detection) was 0.9% for the Treatment group and 3.8% for Control group (posterior probability = 0.9978) using the 90-day maximum for late arrivals. Restricting the analysis to the 7-day maximum gives a 0.8614 posterior probability of superiority.
- None of the other four pre-specified secondary endpoints reached statistical significance. Secondary endpoints in the silent-MI risk subgroup showed approximately 50% relative risk reductions for new Q-wave and a composite of new Q-wave and late arrival.
- Event-based analyses of the primary efficacy endpoint provide additional support of the effectiveness of the Guardian System.
- After unblinding, ECG artifacts were identified in 4 patients that incorrectly identified new Q-wave. When these artifacts were addressed using a “dual baseline” analysis, the primary efficacy endpoint reached a posterior probability of 0.9908 for Treatment group superiority. The relative risk reductions associated with Guardian alarms for secondary endpoints in the silent MI risk subgroup improved to approximately 60%.
- A 157-patient quality of life sub-study found that patients reported significant improvement in their quality of life after alerting features of the Guardian were enabled.

5.1 Patient Disposition

In the ALERTS Study, 1020 patients were enrolled between 2008 and 2013, 910 patients met enrollment criteria and were implanted, and 907 patients were subsequently randomized (Figure

6). The follow-up rate among randomized patients was 97% in the Treatment group and 98% in the Control group.

Figure 6: Disposition of Patients Enrolled in ALERTS



5.2 Patient Demographics and Medical Characteristics

The characteristics of the randomized ALERTS patients are consistent with that of a population at high risk for recurrent ACS events (Table 4), and the two groups were well balanced on demographic and medical characteristics at randomization. The average age was approximately 60 years and approximately one-third of the patients were female. Approximately 98% of patients in ALERTS had a previous revascularization or reperfusion; the prevalence of dyslipidemia, hypertension, diabetes, and significant angina was high.

Table 4: Demographics and Medical Characteristics of Randomized Patients in ALERTS

Characteristic	Treatment Group		Control Group	
	N	Mean ± SD/ n (%)	N	Mean ± SD/ n (%)
Age at Randomization (years)	451	59.4 ± 10.5	456	59.5 ± 10.2
Sex (Female)	451	137 (30.4%)	456	154 (33.8%)
Race/Ethnicity	451		456	
American Indian		0 (0.0%)		1 (0.2%)
Asian/Pacific Islander		5 (1.1%)		2 (0.4%)
Black - Not of Hispanic origin		30 (6.7%)		32 (7.0%)
Caucasian - Not of Hispanic origin		391 (86.7%)		391 (85.7%)
Hispanic		22 (4.9%)		30 (6.6%)
Other		3 (0.7%)		0 (0.0%)

Characteristic	Treatment Group		Control Group	
	N	Mean ± SD/ n (%)	N	Mean ± SD/ n (%)
Presentation of ACS (Qualifying event)	451		456	
STEMI		109 (24.2%)		113 (24.8%)
NSTEMI		126 (27.9%)		127 (27.9%)
Unstable Angina		199 (44.1%)		199 (43.6%)
Other		15 (3.3%)		15 (3.3%)
Unknown		2 (0.4%)		2 (0.4%)
History of Silent MI	451	25 (5.5%)	455	28 (6.2%)
Diabetes	451	206 (45.7%)	456	224 (49.1%)
Dyslipidemia Requiring Medication	451	416 (92.2%)	456	421 (92.3%)
Hypertension Requiring Medication	451	414 (91.8%)	456	426 (93.4%)
History of Smoking	451	322 (71.4%)	456	315 (69.1%)
Currently Smoking	451	117 (25.9%)	456	121 (26.5%)
History of Heart Failure	451	79 (17.5%)	452	60 (13.3%)
NYHA	451		452	
I		34 (7.5%)		18 (4.0%)
II		36 (8.0%)		32 (7.1%)
III		9 (2.0%)		10 (2.2%)
None		372 (82.5%)		392 (86.7%)
Killip Class	446		448	
I		410 (91.9%)		425 (94.9%)
II		34 (7.6%)		20 (4.5%)
III		2 (0.4%)		3 (0.7%)
Ejection Fraction (LVEF, %)	411	54.1 ± 9.4	418	53.9 ± 8.8
History of Renal Insufficiency	451	83 (18.4%)	456	75 (16.4%)
History of Reperfusion/Revascularization	451	442 (98.0%)	456	444 (97.4%)
Angina in previous six months	451	395 (87.6%)	456	400 (87.7%)
Average Frequency of Angina	394		399	
> 10 times/month		58 (14.7%)		63 (15.8%)
6-10 times/month		37 (9.4%)		44 (11.0%)
3-6 times/month		101 (25.6%)		87 (21.8%)
< 3 times/month		198 (50.3%)		205 (51.4%)
Angina Status (most recent episode)	389		398	
Stable		228 (58.6%)		233 (58.5%)
Unstable		161 (41.4%)		165 (41.5%)
History of Silent Ischemic Changes	451		456	
Yes		28 (6.2%)		34 (7.5%)
No		338 (74.9%)		309 (67.8%)
Unknown		85 (18.8%)		113 (24.8%)
TIMI Risk Score (mean)	449	3.7 ± 1.0	454	3.6 ± 1.0
History of Atrial Arrhythmia	450	18 (4.0%)	456	25 (5.5%)
History of Ventricular Arrhythmia	450	25 (5.6%)	456	26 (5.7%)
History of Ectopic Arrhythmia	450	5 (1.1%)	456	6 (1.3%)

Table 5 shows the breakdown of patient characteristics for the silent-MI risk subgroup. Of the entire randomized cohort, 53% of patients in the Treatment group (n=241) and 57% of patients in the Control group (n=261) met criteria for the subgroup by being either diabetic, women over 65 years old, or having experienced prior silent ischemia.

Table 5: Characteristics of Silent MI Risk Subgroup

Criteria	Number of Patients	
	Treatment Group	Control Group
Diabetes	206	224
Female >65 years old	46	46
Prior Silent Ischemia	25	28
Total	**241***	**261***

* Patients may meet more than one criteria

5.3 Primary Safety Endpoint Results

A total of 910 patients were implanted with the Guardian, and 895 patients had evaluable data to assess the endpoint. There were 31 system-related complication events in 30 patients implanted with the Guardian. A summary of each of the events is provided in Table 6.

Overall, the frequency and type of system-related complications is comparable to the rate reported in studies of single-chamber pacemakers.

Table 6: Adjudicated System-Related Complications in ALERTS

Event Type	N Events	N Patients	% of Patients
Infection	11	11	1.2%
Other system-related complication*	5	5	0.5%
Pain at or near the pocket site	4	4	0.4%
Lead migration/dislodgment	4	4	0.4%
Cardiac perforation	2	2	0.2%
Erosion	2	2	0.2%
Loss of sensing due to lead dislodgement/malfunction	2	2	0.2%
Visible bump where implanted in the chest	1	1	0.1%
Total	**31**	**30**	**3.3%**

* These five events include: lead adapter replacement, two early battery failures, patient request for removal due to discomfort, and skin erosion from the lead. The percentage of patients with events was calculated as the number of patients with an event divided by the number of patients implanted with the Guardian System (N=910).

The system-related complication event-free rate was 96.7%. The posterior probability of exceeding the 90% performance goal was >0.9999, so the primary safety endpoint was met (Table 7).

Table 7: Primary Safety Endpoint Results

	Primary Analysis
Event-free patients	880
Patients with events	30
% Event free	96.7% (880/910)
Posterior probability	>0.9999

5.4 Adjudicated Confirmed Occlusive Events

As described in Table 1, confirmed occlusive events are Guardian detections indicative of coronary occlusion that were confirmed by one or more positive tests upon presentation and adjudicated by the independent AGEA Committee. Confirmed occlusive events were used in the calculation of the following efficacy endpoints:

- *Primary efficacy endpoint*: confirmed occlusive events for which the time from occlusion-to-door was greater than 2 hours were counted as "late arrival" events as a component of the composite endpoint
- *Secondary efficacy endpoint (late arrival)*: this "late arrival" component of the composite primary efficacy endpoint was analyzed separately
- *Secondary efficacy endpoint (time-to-door)*: all confirmed occlusive events were analyzed to compare the occlusion-to-door times between groups

At the end of the randomized period of the study, there were 52 confirmed occlusive events (34 events in 27 patients in the Treatment group, and 18 events in 17 patients in the Control group) that had positive tests by cardiac enzymes, ECG, angiography, stress test, or multiple tests. Each of these events had prior associated Guardian ST detection captures (in the Control group) or Emergency Alarms (in the Treatment group). Table 8 provides a summary of the positive tests used to confirm events.

Of note, 94% of events in both groups were confirmed either by cardiac enzymes, ECG, angiography, or multiple tests. Six percent of events (2 Treatment, 1 control) were confirmed by a positive stress test alone; the 2 stress tests in the Treatment group were nuclear stress tests. Stress tests were included as a positive test because they provide a non-invasive method that can identify the residual coronary narrowing following plaque rupture if the thrombus occluding the artery at the time of detection of ST changes has partially resolved.

Comment on Difference in the Number of Events between Groups

The difference in the number of events between the Treatment and Control groups (34 vs. 18) is noteworthy. This imbalance in the number of events was expected given that all confirmed occlusive events required confirmation by a positive test. Due to the high prevalence of risk factors for silent ischemia in this population, it is likely that a number of Control patients did not present at a medical facility in the absence of symptoms to undergo testing. Therefore, at their scheduled follow-up visits, ECG and cardiac enzyme changes that can be seen shortly following an occlusive event would no longer be present. This rationale is further supported by the nearly identical number of Guardian detections of occlusive events in both groups, which triggered an Emergency Alarm in Treatment patients and an ST detection capture in Control patients.

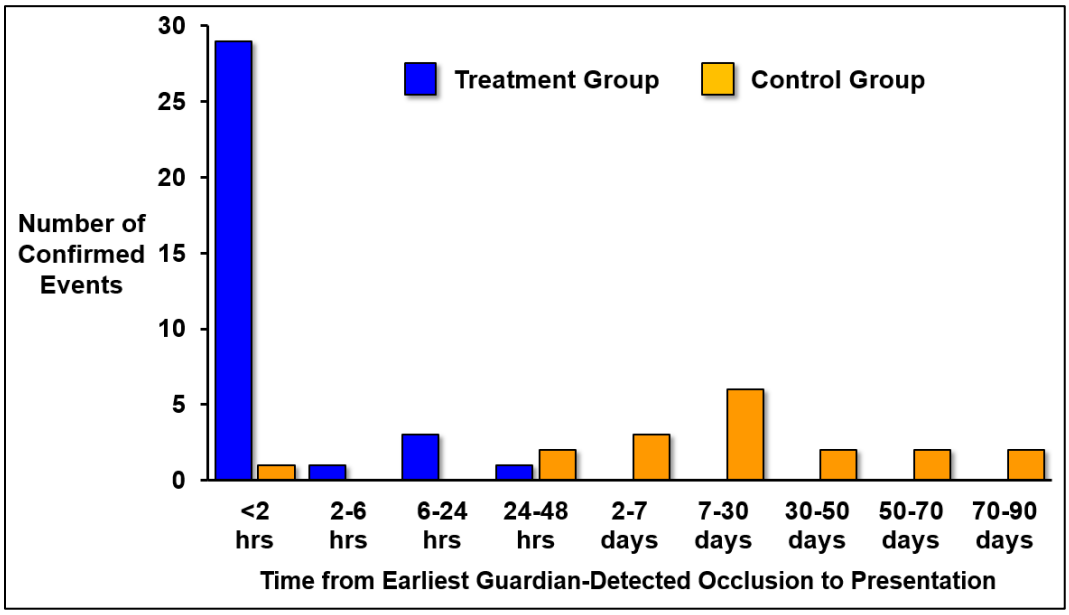
Table 8: Positive Tests Confirming Occlusive Events by Group

Number of Tests	Tests confirming event				Treatment Group (N=34)	Control Group (N=18)
	Cardiac Enzymes	ECG	Angiography	Stress Test		
4	✓	✓	✓	✓	1	0
3	✓	✓	✓		1	2
		✓	✓	✓	3	1
2	✓	✓			6	0
	✓		✓		4	2
		✓	✓		5	1
		✓		✓	1	1
			✓	✓	3	0
1	✓				3	4
		✓			3	5*
			✓		2	1
				✓	2	1

Note: *ECG* denotes blinded ECG core lab identification of ECG changes that indicates an ischemic event. *Angiography* denotes blinded Angiography core lab identification of significant new lesions or thrombus that indicated changes from pre-implant angiograms. * includes 4 events with ST depression or morphological T wave changes, which were not included in the protocol by error.

Figure 7 shows the distribution of occlusion-to-door times for all confirmed events in both groups. Note that for each event, the figure shows the delay between the *earliest* Guardian detection and the patients' presentation for a confirmed occlusive event.

Figure 7: Distribution of Times from Occlusion-to-Door for All Confirmed Events



5.5 Primary Efficacy Endpoint Results

Table 9 illustrates the results of the primary efficacy endpoint analysis with 7-day and 90-day maximum times for late arrivals.

The rate of the composite primary efficacy endpoint was 3.8% in the Treatment group for both 7-day and 90-day maximum times for late arrivals. In the Control group, the analysis for late arrivals using a 7-day maximum does not count 8 patients whose presentation for a confirmed event occurred more than 7 days after a Guardian detection (see Section 5.6.1 for details). The omission of these patients with confirmed events accounts for the discrepancy between the Control group's 4.9% primary efficacy endpoint rate with the 7-day maximum and the 6.8% rate with the 90-day maximum.

The posterior probability of superiority for the Treatment group is correspondingly lower for the analysis using the 7-day maximum for late arrivals (0.7856) than the 90-day maximum (0.9740); however, both fall below the significance threshold of 0.983.

Table 9: Primary Efficacy Endpoint Results in ALERTS

Maximum Time for Late Arrivals	Treatment (N=423) n (%)	Control (N=428) n (%)	Treatment Difference 95% CrI	Posterior Probability
7 Days	16 (3.8%)	21 (4.9%)		0.7856
90 Days	16 (3.8%)	29 (6.8%)		0.9740

Note: CrI = credible interval. Threshold for statistical significance = 0.983. All analyses use the single baseline ECG methodology for assessment of new Q-wave.

5.6 Results for Secondary Efficacy Endpoints

There were six secondary efficacy endpoints. Table 10 presents the secondary endpoint results for the 3 components of the composite primary efficacy endpoint (note: both 7-day and 90-day maximum times for late arrivals are displayed). Each secondary endpoint is discussed individually in the sections that follow.

Table 10: Summary of ALERTS Pre-Specified Secondary Endpoint Results Components of the Primary Endpoint

Secondary Endpoint	Treatment Group		Control Group		Posterior Probability	Posterior Probability >Threshold
	N	n (%)	N	n (%)		
Late arrival >2 hrs. (7-day maximum)	439	4 (0.9%)	446	8 (1.8%)	0.8614	No
Late arrival >2 hrs. (90-day maximum)	439	4 (0.9%)	446	17 (3.8%)	**0.9978**	**Yes**
New Q-wave (single baseline)	420	10 (2.4%)	427	14 (3.3%)	0.7783	No
Cardiac or unexplained death	441	3 (0.7%)	447	1 (0.2%)	0.2524	No

Note: significance threshold based on adjusted posterior probability to control the type-I error rate. **Bold** font indicates that the endpoint met the threshold for statistical significance.

5.6.1 Secondary Endpoint: Late Arrival Component of the Primary Efficacy Endpoint

Using the 7-day maximum for late arrivals, there were 4 patients (0.9%) in the Treatment group and 8 patients (1.8%) in the Control group who had a confirmed event that qualified as a late arrival.

Using the 90-day maximum for late arrivals, no additional confirmed events in the Treatment group were considered late arrivals, as the maximum occlusion-to-door time in the Treatment group was 27 hours. For the Control group, 17 patients (3.8%) were considered as late arrivals. The additional 8 patients with late arrivals in the Control group were due to presentations that occurred more than 7 days following the Guardian detection.

The analysis using the 90-day maximum for late arrivals met the threshold for statistical significance (posterior probability = 0.9978), and the analysis using the 7-day maximum for late arrivals did not (posterior probability = 0.8614).

5.6.2 Secondary Endpoint: New Q-wave Component of the Primary Efficacy Endpoint

The finding of a new Q-wave at six months post-randomization was made using the results obtained by the ECG Core Lab using a single ECG baseline (at randomization). For this component of the composite primary efficacy endpoint, 10 patients (2.4%) in the Treatment group and 14 patients (3.3%) in the Control group met the definition for a new Q-wave. The difference between the groups was not statistically significant (posterior probability = 0.7783).

5.6.3 Secondary Endpoint: Cardiac/Unknown Death Component of the Primary Efficacy Endpoint

There were a total of 6 deaths during the 6-month randomization period. Of these, 3 deaths in the Treatment group and 1 death in the Control group were adjudicated to be either of cardiac or unknown cause, which was not a significant difference (posterior probability = 0.2524)

All three Treatment patients who died of a cardiac/unknown cause had at least one Emergency Alarm or See Doctor Alert prior to their death. For the Control patient, ST changes were detected prior to death that would have triggered an Emergency Alarm, had the alerting feature been activated.

A summary of these deaths is provided in the Appendix II (Section 11). A brief summary of each death is provided below:

- Control patient (*unknown cause of death*): The patient had several ST shift events seen at last follow-up before being found unresponsive. The patient died approximately 2 months after the most recent occlusive event was identified at a scheduled follow-up.
- Treatment patient (*cardiac cause of death*): The patient had 6 Emergency Alarms and presented appropriately for each but did not receive any intervention. The patient died of respiratory arrest.
- Treatment patient (*unknown cause of death*): The patient had multiple Emergency Alarms without symptoms, none of which were followed by intervention. The device was explanted and the patient was transferred to hospice because of heart failure and end stage renal disease. No autopsy was conducted to confirm the cause of death.
- Treatment patient (*cardiac cause of death*): The patient died of cardiac death, although it was not clear whether it was from AMI, primary ventricular tachycardia, or ventricular fibrillation. This patient had received at least one See Doctor alert due to high heart rate. (Note: high heart rates impairs the Guardian's ST segment monitoring functionality.)

5.6.4 Secondary Endpoint: Time-to-Door for Confirmed Events (Occlusion-to-Door Time)

As shown in Table 11, the time from occlusion-to-door was significantly lower in the Treatment group compared to the Control group, independent of the maximum time for late arrivals (posterior probability of superiority >0.9999). Using the 90-day maximum for late arrivals, the median time from occlusion-to-door was 51 minutes in the Treatment group compared to 22 days in the Control group. Even when the presentations after 7 days are omitted using the 7-day maximum for late arrivals, the Control group delay is still considerably longer than the Treatment group (30.1 hours).

This endpoint confirms the efficacy of the Guardian for its designed purpose and proposed indication for use of prompting patients having significant acute ST segment changes indicative of coronary occlusion to take action and arrive quickly at a medical facility independent of the presence of symptoms.

Table 11: Summary of Time-to-Door Endpoint

Maximum for Late Arrivals		Treatment Group (34 events) (27 patients)	Control Group (18 events) (17 patients)	Posterior Probability	Posterior Probability >Threshold?
7 days	N events (N pts)	34 (27)	9 (8)	**>0.9999**	**Yes**
	Mean	2.7 hours	52.3 hours		
	Median	0.85 hrs. (51 min.)	30.1 hrs. (1.3 days)		
90 days	N events (N pts)	34 (27)	18 (17)	**>0.9999**	**Yes**
	Mean	2.7 hours	664.5 hours		
	Median	0.85 hrs. (51 min.)	532.7 hrs. (22 days)		

Note: significance threshold based on adjusted posterior probability to control the type-I error rate. **Bold** font indicates that the endpoint met the threshold for statistical significance.

Comment on Occlusion-to-Door Times

ALERTS is the first study to capture the onset of an occlusion, itself, to measure occlusion-to-door time, rather than the onset of symptoms (i.e., symptom-to-door time). More than half of the patients randomized in ALERTS were at high risk for silent MI. Thus, evidence of a silent event would only be seen upon presentation at a study visit or for an unrelated reason (if evidence of the silent event was still present). The few articles reporting on identification of silent MIs, such as the review conducted by Sheifer et al.,[27] report that it can take months or years before recognition. Furthermore, coronary occlusion is a dynamic process whereby vessels can open and close. As discussed in the Oregon Study even symptoms can come and go – with weeks between the first onset and a recurrence.[26]

Presence of Reported Symptoms at Presentation

Table 12 provides a summary of the presence of reported symptoms at presentation for all confirmed events by treatment group. Symptoms were reported for 15% of confirmed events in the Treatment group compared to 72% of events in the Control group.

This analysis suggests that the Guardian was able to prompt patients to seek medical attention for events that either (a) would have otherwise been silent, or (b) would have been accompanied by symptoms eventually, but the Guardian prompted them to receive medical attention *before* the onset of symptoms.

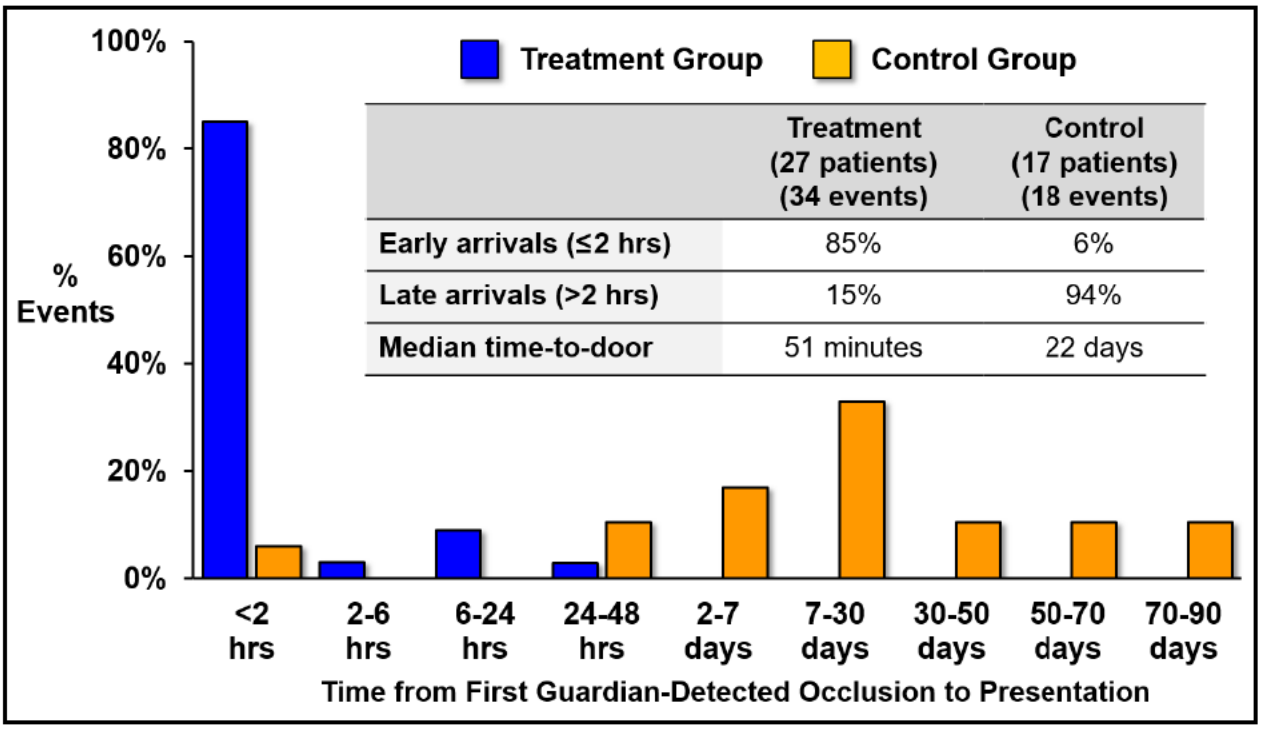
Table 12: Presence of Symptoms for Confirmed Events by Group

	Treatment Group (N=34 confirmed events)	Control Group (N=18 confirmed events)
With Reported Symptoms	5 (15%)	13 (72%)
Without Reported Symptoms	29 (85%)	5 (28%)

Distribution of Early vs. Late Arrivals

Figure 8 summarizes the distributions of arrival times for confirmed events (as a percentage of events) in the Treatment and Control groups using a 90-day maximum for late arrivals. In total, 85% of confirmed events in the Treatment group had arrivals within 2 hours compared to only 6% of events in the Control group.

Figure 8: Summary of Time from First Guardian-Detected Occlusion-to-Door for Confirmed Events (90-day Maximum for Late Arrivals)



	Treatment (27 patients) (34 events)	Control (17 patients) (18 events)
Early arrivals (≤2 hrs)	85%	6%
Late arrivals (>2 hrs)	15%	94%
Median time-to-door	51 minutes	22 days

5.6.5 Secondary Endpoints in the Silent MI Risk Subgroup

Table 13 summarizes the results of the two secondary efficacy endpoints in the silent MI risk subgroup, comprised of patients at high risk for silent ischemia. Although the results for these 2 efficacy endpoints that showed approximately 40-50% relative risk reductions in favor of the Treatment group, neither reached the threshold for statistical significance due to the relatively small number of events. For the composite of new Q-wave or late arrival, results for both 7- and 90-day maximum times for late arrival are displayed. Similar to other analyses, the 7-day maximum excludes several confirmed events.

Table 13: Summary of ALERTS Secondary Endpoints in Silent MI Risk Subgroup

Secondary Endpoint	Treatment Group		Control Group		Posterior Probability	Posterior Probability >Threshold?
	N	n (%)	N	n (%)		
New Q-wave*	222	6 (2.7%)	243	12 (4.9%)	0.8867	No
New Q-wave* or late arrival (7-day maximum)	222	8 (3.6%)	243	14 (5.8%)	0.8542	No
New Q-wave* or late arrival (90-day maximum)	222	8 (3.6%)	243	17 (7.0%)	0.9446	No

* Single baseline analysis for new Q-wave

5.7 Dual Baseline Analysis for the New Q-wave Component of the Primary Efficacy Endpoint and Secondary Efficacy Endpoints

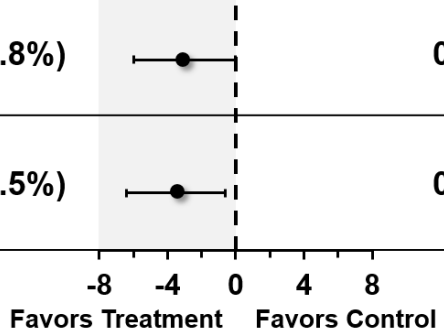
As described in Section 4.7.2, a post-hoc correction to address ECG artifacts was made to ensure that all new Q-waves were accurately identified. There were 4 occasions (3 Treatment patients and 1 Control patient) where pathological Q-waves not present on the randomization baseline ECG, were present on the 6 month follow-up ECG, making them new Q-wave event using the single baseline analysis. However a fully blinded ECG core lab re-read of all ECGs found that these 4 patients had the Q-waves present on the pre-implant ECG. Thus, the pathological Q-waves were not new.

These artifacts were corrected using a "dual baseline" analysis that required both the pre-implant and randomization ECGs to show no evidence of pre-existing pathological Q-waves. Additionally, once evidence of new pathological Q-waves were observed, the Q-waves had to be present at all subsequent visits. This analysis was facilitated by a serial re-read of all ALERTS patient ECGs by the blinded ECG core lab.

The dual baseline primary efficacy endpoint analysis using the 90-day maximum for late arrivals is shown in Table 14, with the single baseline analysis included for comparison. With the 4 false new Q-wave events removed, the posterior probability of 0.9908 exceeds the 0.983 threshold for statistical significance.

Table 14: Single and Dual Baseline Analysis of the Primary Efficacy Endpoint

ECG Baseline	Treatment (N=423) n (%)	Control (N=428) n (%)	Treatment Difference 95% CrI	Posterior Probability
Single	16 (3.8%)	29 (6.8%)		0.9740
Dual	13 (3.1%)	28 (6.5%)		0.9908



Note: 90-maximum for late arrivals. Threshold for statistical significance = 0.983. CrI = credible interval.

Corrections to the affected secondary endpoints using the dual baseline methodology for identification of new Q-wave with a 90-day maximum for late arrivals are presented in Table 15. Although the secondary efficacy endpoints that include the new Q-wave component have higher posterior probabilities in dual baseline analysis than single baseline analysis, none achieved statistical significance due to the relatively modest number of events. So while not significant, it is interesting to note that the two endpoints for the silent MI risk group show ratios of approximately 3 to 1 comparing Control to Treatment (i.e., an approximate 60% relative risk reduction), and an approximate 2 to 1 ratio for new Q-wave overall.

Table 15: Summary of Secondary Efficacy Endpoint Results Using Dual Baseline Analysis

Secondary Endpoint	Treatment Group		Control Group		Posterior Probability	Posterior Probability >Threshold?
	N	n (%)	N	n (%)		
New Q-wave (all patients)	420	7 (1.7%)	427	13 (3.0%)	0.9015	No
New Q-wave (silent MI risk subgroup)	222	4 (1.8%)	243	11 (4.5%)	0.9470	No
New Q-wave or late arrival (silent MI risk subgroup)	222	6 (2.7%)	243	16 (6.6%)	0.9741	No

Note: significance threshold based on adjusted posterior probability to control the type-I error rate. **Bold** font indicates that the endpoint met the threshold for statistical significance.

5.8 Event-based Analyses of the Primary Efficacy Endpoint

While the pre-specified primary efficacy endpoint was analyzed on a patient basis (where each patient can only count as one primary efficacy endpoint event), the FDA requested an event-based analysis during the review of the PMA. Two different types of analyses were undertaken in order to address this request:

- An "event-based" analysis where each qualifying primary endpoint event (i.e., new Q-wave, cardiac or unknown death, late presentation for a confirmed event) was counted in the analysis (when multiple events occurred in the same patient).
- A "Guardian detection-based" analysis where each Guardian capture of an occlusive event preceding presentation with a positive test was counted as distinct events in the primary endpoint analysis. In other words, if a patient had 2 Guardian detections prior to a presentation where a coronary event was confirmed, this would count as 2 events in the analysis.

For each analysis, results using the 90-day maximum for late arrivals as well as single and dual baseline ECG methodologies are presented in Table 16. Overall, each of the analyses that incorporated multiple events or detections provided additional support for the benefit of alarms with regard to the primary endpoint since most of the additional events occurred in the Control group.

Table 16: Event- and Detection-based Analyses of the Primary Efficacy Objective

Analysis	Group	N Events	Rate (events / patient-year)	Rate Ratio 95% CrI	Posterior Probability
Event-based Analysis					
Single ECG Baseline	Control	32	0.148	0.558 (0.310, 0.985)	0.9779
	Treatment	18	0.082		
Dual ECG Baseline	Control	31	0.143	0.480 (0.255, 0.877)	0.9918
	Treatment	15	0.069		
Detection-based Analysis					
Single ECG Baseline	Control	41	0.189	0.436 (0.247, 0.749)	0.9989
	Treatment	18	0.082		
Dual ECG Baseline	Control	40	0.184	0.372 (0.202, 0.662)	0.9997
	Treatment	15	0.069		

5.9 Patient Acceptance

An indication of patients' feelings about the benefits of the Guardian System can be seen objectively in their willingness to undergo a revision procedure to replace the Guardian IMD when its battery reached end-of-life. As of the database lock date, 175 patients were eligible for re-implant and were asked if they wanted a replacement. Upon patient request, 93% (163/175) patients underwent IMD replacement and only 7% (12/175) were explanted.

5.10 AQOL Quality-of-Life Sub-Study

The ALERTS Quality-Of-Life (AQOL) sub-study was designed and run as an independent study among patients randomized in the ALERTS Study during the two final years of the study. The sub-study was designed to assess patients' reported quality of life.

The AQOL sub-study enrolled a subset of 157 patients in the ALERTS Study in order to prospectively examine changes in QOL by comparing the patient's quality-of-life prior to implantation to their quality-of-life at both 6 and 12 months after their Guardian's alerting features were activated. These time points coincide with 6 and 12 months after randomization for Treatment patients and 12 and 18 months after randomization for Control patients, as Control patients did not have the alerting feature of the Guardian enabled until 6 months following randomization.

The sub-study employed a repeated-measures design, using each patient's baseline values as their own control. A between-subject design was not suitable because patients were not blinded to their randomization assignment, so between-group differences in QOL could be confounded by differential feelings of displeasure of being randomized to the Treatment or Control group.

The AQOL study administered two well-established, validated QOL instruments, the EuroQOL[28,29] and MacNew,[30-32] and a customized QOL survey (AMQOL). The EuroQOL is a general health-related QOL instrument. The MacNew is designed specifically for evaluation of heart-related medical interventions. The AMQOL was a custom survey commissioned by AngelMed to query about QOL aspects unique to the Guardian that were not assessed by the validated surveys.

- *EuroQOL*: Improvements in the EuroQOL were significant and sustained at both 6 and 12 months after alerting was enabled ($p<0.01$).
- *MacNew:* Improvements in the MacNew, which is more relevant for assessing cardiac QOL, also demonstrated statistically significant improvement from baseline at 6 and 12 months ($p<0.0001$).
- *AMQOL:* Most of the measures showed significant improvement in QOL, particularly those regarding having more control with alerting turned on, with 90% feeling safer with alarms, and having less anxiety overall.

AQOL Summary: Given the fact that the sub-study was limited to 157 ALERTS patients, the sub-study results cannot be generalized to the entire ALERTS cohort. AngelMed interprets the statistically significant improvements in QOL as encouraging, and that the data support the contention that the Guardian System was well accepted by patients and does not have a negative impact on patients' QOL.

6 DEVICE PERFORMANCE AND PERCEIVED RISKS OF ALERTING

Summary

- Positive predictive value (PPV) was used at the request of FDA to evaluate the accuracy of device detections.
- Two event definitions were used to evaluate the PPV of Guardian Emergency Alarms:
  - ACS events (see definitions in Section 4.4)
  - ACS events with other medically relevant conditions (bundle branch block, sleep apnea, and vasospasm/transient coronary occlusion)
- The estimated PPV of Guardian Emergency Alarms for ACS events was 65%. The estimated PPV of Emergency Alarms for ACS events with other medically relevant conditions was 77%. Both results compare favorably to the PPV of chest pain for AMI/ACS reported in the literature, which is approximately 15-20%.
- Three of the 5 STEMIs that occurred during the randomization period in both groups had a prior Guardian detection (Control) or Emergency Alarm (Treatment). Two of the 5 detections of STEMIs occurred after presentation (15 min [Treatment] and 13 hrs [Control]).
- Several perceived risks of alerting that were of concern prior to the start of the ALERTS Study proved not to be true:
  - Guardian alarms did not cause an excessive number of unneeded cardiac catheterizations.
  - Patients responded to alarms appropriately and in a timely fashion.
  - Patients who had an Emergency Alarm were able to be accommodated in the emergency department using hospitals' standard-of-care chest pain protocols.

6.1 Positive Predictive Value (PPV)

In the course of review of the PMA application, the FDA requested an analysis to assess the accuracy of Guardian Emergency Alarms. The ALERTS Study protocol did not specify a process or requirement associated with sensitivity and specificity for the performance of alarms.

After discussions with the FDA, an analysis of the positive predictive value (PPV) was determined to be the most sensible approach to assessing Emergency Alarm accuracy because it is possible to measure when an Emergency Alarm occurs and when an ACS event is detected at the emergency department. For this PPV analysis, definitions for “true positive” and “false positive” alarms were agreed upon:

- A “confirmed positive alarm” (CPA) was defined as an occurrence of an Emergency Alarm where an ACS event was detected upon presentation at the emergency room. This is considered a “true positive”.
- A “non-confirmed positive alarm” (NCPA) was defined as an occurrence of an Emergency Alarm where an ACS event was not detected upon presentation at the emergency room. This is considered a “false positive”.

The definition of an ACS event (see Table 1) and further specification of which alarms should be included in the analysis of PPV were agreed upon with the FDA.

In addition to the events captured in the definition for ACS, AngelMed contends that three other types of events, which were either diagnosed or indicative of medical conditions, were also clinically meaningful and are valuable for patient care:

- **New identification of rate-induced bundle branch block (BBB)** which produces waveforms with ST segment changes sufficient to trigger an Emergency Alarm. BBB emergence is a change in cardiac status that doctors may wish to know. Additionally, BBB was an exclusion criterion for the ALERTS Study, so these detections were newly diagnostic.
- **Sleep apnea that produced sufficient cardiac ischemia to trigger an Emergency Alarm.** Detection of a patient where severe sleep apnea induced severe acute ST-interval changes is relevant due to the literature on increased sudden death in this patient population.
- **Vasospasm or transient thrombotic occlusion with significant ST waveform changes identified by the Guardian that were not confirmed by positive tests.** The Guardian electrograms related to these alarms showed waveforms having significant ST segment changes indicative of transmural ischemia that are reflective of vasospasm and well documented in the literature.[33] Such literature indicates that transient episodes may resolve without complications, but arrhythmias, syncope, MI, and sudden death can occur. In particular, it is stated that vasospastic angina can occasionally cause AMI. For this reason, early detection of these events can provide a clinical benefit to patients, particularly the high-risk target population of the Guardian System.

Over the 6-month randomization period, there were 92 Emergency Alarms that were characterized as CPA or NCPA in the Treatment group (Table 17).

- Using the ACS definition, there are 60 CPAs and 32 NCPAs.
- Using the definition for ACS events with other medically relevant conditions, there are 70 CPAs and 22 NCPAs.

Table 17: Confirmed Positive Alarms (CPA) and Non-Confirmed Positive Alarms (NCPA) for Different PPV Assessments in the Treatment Group

PPV Assessment		Count	Alarm Code Event Type
ACS	ACS + other events		
CPA	CPA	60	Confirmed Positive Alarm (Stress/ECG/Enzyme/Site Cath/Core Lab ECG/Core Lab Angio)
NCPA	CPA	4	Other Relevant Medical condition (i.e., BBB)
NCPA	CPA	5	Vasospasm Transient Ischemia
NCPA	CPA	1	Sleep Apnea Non-compliance
NCPA	NCPA	1	Algorithm Anomaly Not Corrected
NCPA	NCPA	14	Negative for Stress/ECG/Enzyme/Site Cath/Core Lab ECG/ Core Lab Angio
NCPA	NCPA	3	Lead dislodgement, Improper Connection, Device Problem
NCPA	NCPA	4	Symptoms only (no confirmatory tests)
		92	Total

Among the 14 NCPAs that were considered "negative" for all tests include: 3 events in one patient with a bigeminal rhythm, 3 events with ST depression seen on the electrogram from demand ischemia where the patient's heart rate was on the border between normal and elevated heart rate. The cause for the remaining 8 negative events were not clearly identified. Four (4) Emergency Alarms without positive tests, but with associated symptoms, are counted as NCPAs.

In addition to a raw count analysis, generalized estimating equations (GEE) with robust variance estimation and an exchangeable working correlation structure were used to calculate PPV in a manner that accounted for within-patient correlation.

Table 18: Positive Predictive Value (PPV) Calculations

Method	PPV Raw Count Point Estimate	PPV Model-Based Point Estimate (95% CI)
ACS	65.2% (60/92)	65.3% (54.2%, 74.9%)
ACS with other medically relevant conditions	76.1% (70/92)	77.4% (67.0%, 85.2%)

In the absence of any other technology for alerting patients to an AMI/ACS event, chest pain is the most appropriate comparator to the Guardian as a prompt for patients to seek medical treatment for an ACS or AMI event. The 65% to 77% PPV of Guardian Emergency Alarms for ACS events is a considerable improvement over the 14% to 21% PPV of chest pain for AMI or AMI/ACS events reported historically in the literature.[17,19,34,35]

6.2 Perceived Risks of Alerting

Perceived risks of the Guardian alerting to cause potential safety issues existed at the beginning of the study and has been a topic of inquiry from the FDA. Specifically, these perceived risks included:

1. Emergency alarms without chest pain/other physical symptoms would lead to a high number of unnecessary cardiac catheterizations.
2. Patients would ignore alarms or would not respond to alarms quickly enough to provide a significant improvement in arrival time at a medical facility.
3. Emergency departments would be confused as to how to provide an appropriate standard of care when patients with a Guardian alert arrived.

The ALERTS study provided the needed data to address these concerns:

1. **Emergency Alarms, specifically those without associated symptoms, did not cause a large number of unnecessary cardiac catheterizations.** Of the 76 catheterizations performed in Treatment patients as a result of an emergency room presentation, 24 (32%) were conducted for alarms-only (i.e., without the presence of symptoms), which is a rate that is comparable to the rate of silent MIs reported in the literature. Only 3 of the cardiac catheterizations for alarms-only were not associated with an ACS event, giving a low rate of unnecessary cardiac catheterizations overall (3/451, 0.66%); and, none of the 3 catheterizations led to any adverse clinical sequelae.
2. **Patients did not ignore alarms and responded promptly.** For AGEA-adjudicated confirmed events with positive tests, 85% (29/34) of arrivals occurred within 2 hours of the alarm, and the latest arrival for a confirmed event was 27 hours.
3. **Emergency Alarms were appropriately incorporated into current standard-of-care in emergency departments.** Based on data from more than 100 participating centers, standard chest pain protocols have been shown to be effective in evaluating the condition of patients presenting due to symptoms alone, symptoms plus alerting, or alerting alone (e.g., 12-lead ECG changes, cardiac enzymes). The primary role of the Guardian System is to prompt patients, with or without symptoms, to arrive at the emergency department earlier than they would have had there been no such alarm.

In summary, the perceived risks of alerting were not supported by the ALERTS Study data. The risks associated with the Guardian System, therefore, are limited to the system-related complications that were captured in the primary safety endpoint, which are relatively low and well understood from decades of pacemaker implantation.

7 POST-MARKET REGISTRY PROPOSAL AND TRAINING PLANS

7.1 Post-Market Registry Study Proposal

The ALERTS Study has demonstrated that the AngelMed Guardian System prompted high-risk patients to seek medical attention for coronary occlusive events in a timely manner, largely independent of recognized symptoms.

AngelMed proposes to continue capturing information on key metrics in a similar high-risk patient population in the post-marketing environment to increase the size of the population (and incidence of relatively rare events) to capture clinical outcome metrics based on what was learned from the ALERTS Study. In order to achieve this goal, AngelMed proposes a prospective, event-driven, post-market registry study with an appropriate control group. The enrollment and closure of the registry would be determined in a dialogue with FDA to ensure adequate precision is attained for all endpoints in the study. AngelMed is planning to have patients enrolled in the post-market study to be included in the American College of Cardiology's ACTION Registry which is already directed at measuring outcomes for patients experiencing STEMI or NSTEMI.

The following metrics are being proposed for the post-market registry study:

- Time from occlusion-to-door for qualified ACS events
- Patient Emergency Alarm compliance
- PPV for qualified Emergency Alarms
- Assessment of preservation of LVEF using a standardized protocol
- Identification of new Q-waves from using dual baselines
- 1-year mortality following recurrent STEMI/NSTEMI
- Safety data related to initial implant and replacement procedures

7.2 Proposed Post-Market Training Program

AngelMed proposes that the training program in the post-market setting use a model similar to that used for the ALERTS Study, which was successfully deployed to over 100 sites in the United States and Europe.

The training program will focus on education for three primary groups of medical personnel:

- Emergency Medical Technicians (EMTs) and paramedics – these individuals will be trained to understand the purpose of the Guardian device, how it works, and what should be done when they encounter patients experiencing an alarm. They will also be informed that the Guardian is a monitoring device only and that it does not deliver any electrical therapy.
- Emergency Department Personnel (including cardiologists) – these individuals will receive the same training as EMTs, but also be trained on how to interrogate the

Guardian IMD, and how to incorporate the data retrieved from the Guardian IMD into the current standard of care in their hospital.

- Coronary Care Practitioners (including electrophysiologists, interventional cardiologists, and the same clinical staff tasked with programming ICDs and pacemakers) – these individuals will receive the same training as EMTs and emergency department personnel, along with information regarding how to program the device and conduct follow-up activities (e.g., patient training and re-training, changing the EXD battery), how to retrieve data from the IMD, and how to review Guardian data on heart rate and other medically relevant cardiac metrics.

If approved, the distribution of the Guardian System will be controlled to ensure that the device is used safely and appropriately at all implanting centers. The Guardian will initially be distributed to clinical sites that participated in the ALERTS Study that are willing to participate in the post-market study. As additional sites are trained, programmers will be distributed at participating sites and local hospitals, similar to the model used to support programmers for pacemakers and ICDs.

8 BENEFIT-RISK ASSESSMENT

The Guardian System is a first-in-class technology that addresses a long-standing unmet need in cardiology. The Guardian System markedly improves the time to treatment for patients with coronary occlusion – regardless of whether symptoms are present or not.

As the Guardian System approaches its 11th year of clinical testing and the final PMA review by the FDA, more than 2,000 patient years of data have now been collected. The totality of the data demonstrate that the Guardian System is safe, effective, and has a positive benefit-risk profile for its proposed indication to "*reduce the overall time-to-door from a detected coronary occlusion until presentation at a medical facility with or without associated symptoms*" for high-risk patients with prior acute coronary syndrome events.

The sections below summarize the key findings in support of each claim for safety, efficacy, and overall benefit-risk:

Safety

- The ALERTS Study easily met its primary safety objective at an extremely high level of probability (>0.9999).
- The risks of the Guardian System are low, with the well-known safety profile of a single-chamber pacemaker.
- The ALERTS Study demonstrated that the perceived risks of alerting that existed prior were not supported.

Efficacy

- The patient response times for confirmed coronary occlusive events were significantly faster for patients in the Treatment group who had the benefits of alerting compared to the Control group who did not.
  - The median time from occlusion-to-door for confirmed occlusive events was 51 minutes in the Treatment group compared to 22 days in the Control group. The 51-minute median time from occlusion-to-door in the Treatment group surpasses the best results ever seen in any prior study of patient symptom-to-door times.
  - Considering a goal of “early arrival” within 2 hours of a confirmed coronary occlusion, 85% of events in the Treatment group achieved this goal compared to only 6% of events in the Control group.
  - Faster times to presentation were independent of whether patients experienced recognized symptoms. Differential reports of symptoms at presentation for confirmed events between the groups suggests that Guardian alarms prompted patients to respond to occlusive events (1) that would have otherwise been silent or (2) prior to the onset of symptoms that would have occurred had the patient not been alerted.
- Emergency Alarms are several times more accurate at recognizing acute coronary syndromes than chest pain – currently the best prompt patients have to seek treatment.
- Re-implant rates following end-of-battery life suggest excellent patient acceptance of the technology.

Overall Benefit-Risk Assessment

Timely presentation to a medical facility following onset of a heart attack constitutes a major unmet clinical need. The two greatest obstacles in the administration of effective care are patient delay in the presence of recognized symptoms and patient recognition in the absence of symptoms. Chest pain, the most well-recognized and common symptom of a heart attack is not a sensitive, specific, or timely prompt for patients to seek treatment.

The ALERTS Study, like a number of historical studies, has illustrated how ineffective symptom recognition is as a prompt for patients who experience a coronary occlusion to seek treatment quickly. The Control group in the ALERTS Study represents the current "real-world" response to coronary occlusion in a patient population at high risk for a recurrent ACS event. Many of these patients present long after the coronary blockage could have been detected and treated, with extremely high costs to patients' health and the medical system.

The Guardian System is the first technology to solve this problem. The ALERTS Study has unequivocally demonstrated the Guardian's ability to reduce the time from onset of a coronary occlusion to patients' presentation at a medical facility for treatment. As such, the Guardian represents a paradigm shift in the treatment of coronary occlusive events from a *reactive* approach to a *proactive* one. The Guardian provides a new ability to detect serious cardiac events that cause high morbidity and mortality, where earlier intervention can change the disease process, making an important impact on both individual patients and public health.

The data from the ALERTS trial provides important new information related to patient behavior following the onset of a coronary occlusion. The post-marketing environment will offer additional opportunities to study the full capability and clinical benefits of the Guardian System.

The AngelMed Guardian System is the first technology that provides a prompt for coronary occlusive events that occur with or without recognized symptoms and addresses the well-known problem of patient delay in presentation to a medical facility. The clear efficacy for its designed purpose and the limited associated risks support approval of the Guardian for its proposed indication and intended use.

9 REFERENCE LIST

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.

2. Thune JJ, Signorovitch JE, Kober L, et al. Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction. Eur J Heart Fail 2011;13:148-53.

3. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109:1223-5.

4. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. Circulation 2009;119:1330-52.

5. Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Arch Intern Med 2010;170:1842-9.

6. Ting HH, Chen AY, Roe MT, et al. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. Arch Intern Med 2010;170:1834-41.

7. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986;1:397-402.

8. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. J Am Coll Cardiol 1988;12:3A-13A.

9. Canto JG, Zalenski RJ, Ornato JP, et al. Use of emergency medical services in acute myocardial infarction and subsequent quality of care: observations from the National Registry of Myocardial Infarction 2. Circulation 2002;106:3018-23.

10. Faxon D, Lenfant C. Timing is everything: motivating patients to call 9-1-1 at onset of acute myocardial infarction. Circulation 2001;104:1210-1.

11. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993;328:673-9.

12. Gibson CM. Reducing time delays in patients with ST elevation MI. Satellite symposium of the Heart Rhythm Society. Boston, MA2009.

13. McAlister FA, Quan H, Fong A, Jin Y, Cujec B, Johnson D. Effect of invasive coronary revascularization in acute myocardial infarction on subsequent death rate and frequency of chronic heart failure. Am J Cardiol 2008;102:1-5.

14. Newman JD, Muntner P, Shimbo D, Davidson KW, Shaffer JA, Edmondson D. Post-traumatic stress disorder (PTSD) symptoms predict delay to hospital in patients with acute coronary syndrome. PLoS One 2011;6:e27640.

15. Voigt J, Sasha John M, Taylor A, Krucoff M, Reynolds MR, Michael Gibson C. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol 2014;37:312-21.

16. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. J Am Coll Cardiol 2000;36:2056-63.

17. Bright H, Pocock J. Prehospital recognition of acute myocardial infarction. CJEM 2002;4:212-4.

18. Burgess DC, Hunt D, Li L, et al. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Eur Heart J 2010;31:92-9.

19. Goodacre S, Locker T, Morris F, Campbell S. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? Acad Emerg Med 2002;9:203-8.

20. Gibson CM. Time is myocardium and time is outcomes. Circulation 2001;104:2632-4.

21. Fischell TA, Fischell DR, Fischell RE, et al. Potential of an intracardiac electrogram for the rapid detection of coronary artery occlusion. Cardiovasc Revasc Med 2005;6:14-20.

22. Krucoff MW, Parente AR, Bottner RK, et al. Stability of multilead ST-segment "fingerprints" over time after percutaneous transluminal coronary angioplasty and its usefulness in detecting reocclusion. Am J Cardiol 1988;61:1232-7.

23. Fischell TA, Fischell DR, Avezum A, et al. Initial clinical results using intracardiac electrogram monitoring to detect and alert patients during coronary plaque rupture and ischemia. J Am Coll Cardiol 2010;56:1089-98.

24. Fischell TA, Fischell DR, Fischell RE, Virmani R, DeVries JJ, Krucoff MW. Real-time detection and alerting for acute ST-segment elevation myocardial ischemia using an implantable, high-fidelity, intracardiac electrogram monitoring system with long-range telemetry in an ambulatory porcine model. J Am Coll Cardiol 2006;48:2306-14.

25. Day MCY, C. "This is your heart speaking. Call 911.". Ergon Des Q Human Factors Appl 2012;20:4-12.

26. Marijon E, Reinier K, Evanado A, Teodorescu C, Narayanan K. Abstract 18987: Warning symptoms precede sudden cardiac death in majority of men. American Heart Association Scientific Sessions. Dallas, TX2013.

Now published as: Marijon E, Uy-Evanado A, Dumas F, et al. Warning symptoms are associated with survival from sudden cardiac arrest. Ann Intern Med 2016;164:23-9.

27. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. Ann Intern Med 2001;135:801-11.

28. Ellis JJ, Eagle KA, Kline-Rogers EM, Erickson SR. Validation of the EQ-5D in patients with a history of acute coronary syndrome. Curr Med Res Opin 2005;21:1209-16.

29. Nowels D, McGloin J, Westfall JM, Holcomb S. Validation of the EQ-5D quality of life instrument in patients after myocardial infarction. Qual Life Res 2005;14:95-105.

30. Dixon T, Lim LL, Oldridge NB. The MacNew heart disease health-related quality of life instrument: reference data for users. Qual Life Res 2002;11:173-83.

31. Hofer S, Lim L, Guyatt G, Oldridge N. The MacNew Heart Disease health-related quality of life instrument: a summary. Health Qual Life Outcomes 2004;2:3.

32. Oldridge N, Guyatt G, Jones N, et al. Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. Am J Cardiol 1991;67:1084-9.

33. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344-426.

34. Grosmaitre P, Le Vavasseur O, Yachouh E, et al. Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments. Arch Cardiovasc Dis 2013;106:586-92.

35. Schillinger M, Sodeck G, Meron G, et al. Acute chest pain--identification of patients at low risk for coronary events. The impact of symptoms, medical history and risk factors. Wien Klin Wochenschr 2004;116:83-9.

10 APPENDIX I: ALERTS STUDY INCLUSION/EXCLUSION CRITERIA

10.1 ALERTS Study Inclusion Criteria

Inclusion Criteria

All of the following criteria must be present:

1. Patient has at least one of the following conditions:
    a. Diabetes (Type I or Type II)
    b. Compromised renal function (Cr > 1.2 mg/dl or creatinine clearance less than 50)
    c. TIMI Risk Score > 3
2. Presents (within past 6-months) with a high-risk acute coronary syndrome (e.g., Unstable Angina, STEMI or NSTEMI) or has undergone or is scheduled for CABG within 6-months of implantation.
3. Has already undergone coronary angiography and revascularization, unless the physician determines it is appropriate to implant before or during the planned procedure.
4. Lives in a geographic area in close proximity (within 60 minutes by EMS) to any hospital that can treat AMI.
5. Patients (men or women) at least 21 years of age. Women of childbearing age must have a negative pregnancy test or confirmation of one of the following:
    a. Post-menopause or amenorrheic during the past year
    b. Surgical sterilization
    c. Use of effective contraceptive method

10.2 ALERTS Study Exclusion Criteria

Candidates will be excluded from the study if ANY of the following conditions apply:

1. In the investigator's opinion, patient lacks ability to respond appropriately to alarms, e.g., illiteracy, poor memory or cognitive function, dementia or other condition affecting memory function, etc.
2. There is known compromised tissue at the site of lead implantation in the apex of the right ventricle, e.g., prior infarct affecting the RV apex location.
3. A permanent pacemaker or ICD is already in place or the patient is indicated for ICD or pacemaker implantation based on the guidelines published by the American College of Cardiology as Class I and IIa recommendations. Class IIb recommendations are at the investigator's discretion.
4. Patient cannot feel the IMD vibration when placed on top of the skin on the left pectoral side of the chest.
5. Patient has recurrent or persistent atrial fibrillation.
6. Patient has recurrent or persistent non-sinus cardiac rhythm, second or third degree atrioventricular blocks, QRS duration greater than 120 ms, Benign Early Repolarization (BER), or Brugada Syndrome.
7. Patient has left ventricular hypertrophy evidenced by EKG criteria.
8. Patient has any condition preventing the subcutaneous implantation of the Guardian System in a left pectoral pouch, such as: superior vena cava thrombosis, subcutaneous tissue deemed inappropriate for the procedure or prior central venous access via portacath, Hickman, Groshong, or similar placed in a left pectoral location or left side PICC line.
9. Patient has extremely heavy alcohol consumption (participates in binge drinking that leads to alcohol intoxication) or has history of alcohol or illicit drug abuse within past 5 years.
10. There is evidence of unresolved infection (fever > 38° C and/or leukocytosis > 15,000).
11. Patient has history of bleeding disorders or severe coagulopathy (platelets < 100,000 plts/ml; APTT or PT > 1.3 x reference range).
12. Patient has had a hemorrhagic stroke or transient ischemic attack (TIA) in the past 6-months.
13. Patient has other severe diseases, such as cancer or refractory congestive heart failure, associated with limitation of life expectancy (less than 1 year), which may lead to inadequate compliance to the protocol or confusing data interpretation.
14. Patient has clinical conditions such as heart diseases, difficult-to-control blood pressure, difficult-to-control insulin-dependent diabetes or serious prior infections attributed to the diabetes, or others that, at the investigator's discretion, could seriously affect the patient's current clinical condition during study procedures.

15. Patient has previous participation in the DETECT Study, current participation or previous participation in another drug or device study in the past 30 days that conflicts with this study as determined by the study sponsor.
16. Patient has experienced gastro-intestinal hemorrhage in the past 6-months.
17. Patient has any situation in which the use of aspirin is contraindicated for at least 6-months.
18. Patient has epilepsy.
19. Patient has known severe allergies, e.g., peanut, bee sting, etc.

11 APPENDIX II: DEATH CLINICAL SUMMARIES

The sponsor was not involved in the adjudication of death events – that was performed by the AC (Adverse Events Committee). The Chief Medical Officer of Angel Medical and Director of Cardiovascular Research at Borgess Heart Institute, Dr. Tim A. Fischell, has summarized the 4 deaths as follows:

Case 1-(b) (5) (Treatment)

Review: This is a death of a patient in treatment group. The patient was enrolled as a 61 year old woman with multiple, and severe medical problems including diabetes, hypertension, and hyperlipidemia, as well as known advanced coronary artery disease. She had undergone prior bypass surgery and two previous stent revascularizations procedures. She was enrolled into the treatment arm of the ALERTS Protocol following an episode of unstable angina in September 2012. She had had a stent placed in July of 2012. Of note, she was still at some high risk due to her diabetes prior coronary artery disease and a moderate control of her hyperlipidemia. At the time of enrollment she was having NYHA class 3 angina that was treated medically. Of note, she had had a total of six ST shift events that were alerted and alarmed due to high heart rate with ST segment shifting prior to her three-month visit in December 2012. No further intervention was performed despite these ST segment shift events. She was otherwise relatively stable with some angina until 1-25-13 when she began to have problems with her breathing. She was with her niece and complained of being tired and short of breath. She went to bed but then was awakened at 3 am on 1-26-13 with severe shortness of breath. This progressed to a full respiratory arrest and ultimately asystole, despite CPR and resuscitation at the hospital.

Resuscitated efforts were unsuccessful and the patient died. No autopsy was performed. AngelMed was not informed of the death until four days after the event. As such, the device could not be retrieved. It is not entirely clear whether the patient had received any alerts prior to her passing. It is also not clear that this was necessarily an acute MI or an arrhythmic, event although this remains a possibility. The patient had previously experienced chest discomfort with ischemia and therefore the fact that she was only complaining of shortness of breath (no chest pain) makes it less clear that this was an acute or an occlusive or sub-occlusive coronary artery event. On the other hand, she had had multiple ST shifts with elevated heart rate alerts that were never acted upon by her physicians suggesting that she may have had ongoing obstructive coronary artery disease and some level of ischemia.

Summary: This was a 61 year old with an apparent cardiovascular death ~ 5 months after enrollment into the treatment arm of the ALERTS Study. This is most likely a death related to ischemia and/or acute congestive heart failure. It is not certain that this was an acute ST segment elevation MI event, based on the reporting from the paramedics, and based on the failure to confirm this via a retrieval of data from the Guardian device.

Case 2-(b) (5) (Control)

Review: The patient was enrolled into the ALERTS Study in October 2011. The patient was an 83 year-old woman with known coronary disease, hypertension, hyperlipidemia, and diabetes as well as positive family history for coronary disease. She had undergone prior stenting for severe coronary obstructive disease. She presented in October 2011 with unstable angina she had had a prior MI. The Guardian device was implanted on 10-18-11. The patient was randomized to be in the control and non-alerting group. At one-month follow up the patient had downloads indicating two emergency alerts for ST shift without a change in heart rate that would be indicative of a severe coronary obstructive event. The patient also had multiple "see doctor" alerts for irregular heart rates. She had an additional set of "see doctor" alerts at three months. On February 6, 2012 she was found dead in her bedroom in her apartment at a retirement ranch. No autopsy was performed. There was no ability to interrogate the device for an ST segment shift event prior to the death because of the flat-line recordings that filled the memory space in the Guardian device that occurred following death.

Summary: This was an 83 year old woman with known severe coronary artery disease and multiple risk factors with at least one prior MI and a moderately reduced ejection fraction status post five prior stent implants who was enrolled into the ALERTS Study, and randomized to the control group (without alerting). She had a number of ST segment shift events that would have alerted her with emergency alerts for possible plaque rupture and vessel occlusive events but these were non-alerting events because of her randomization to the control group. At approximately two months following her most recent ST segment shift detection by the Guardian device, she was found unresponsive and passed away at her home. Although the official cause of death is unknown, it is more likely than not that this could have been a cardiovascular event, including a ST elevation MI event given the prior emergency recordings from the Guardian device at the one and three month follow up visits.

Case 3-(b) (5) Treatment)

Review: Patient was in the treatment group and the cause of death is officially adjudicated as a cardiac death. This patient was enrolled into the ALERTS Study on March 8, 2013. He was a 62 year-old male at the time of enrollment. He had relatively severe risk factors including very elevated total cholesterol of 307 with an HDL of 31 giving him a ratio of approximately 10. He presented with STEMI on January 4, 2013 prior to the enrollment of the study. This was an anterior MI. He had sustained a total of two MIs, including the STEMI in January 2013. He had an LVEF of 45% as well as the history of hypertension and a remote history of smoking, and a history of renal insufficiency with a creatinine of greater than 2.0. He had undergone prior stenting and prior bypass surgery with his most recent stent in January 4, 2013 in the setting of his anterior MI. The Guardian implant was performed on March 21, 2013. Between April 2013 and August 2013, when the device was explanted, the patient had multiple emergency alerts. This included asymptomatic ST shift on April 17, asymptomatic ST shift emergency alarms on April 27, and through the 30th, asymptomatic emergency alarm shift on May 28, as well as multiple ST segment shift trend events between June 8-13 and between August 25-30. Prior to explant he had additional ST segment shift emergency alarm. None of these events were acted upon with a repeat heart catheterization. The records show the patient was viewed to be in an end stage situation due to his cardiovascular and renal disease, and therefore no further interventions were performed following his MI. The patient felt to be in a terminal condition at the time of explant and was transferred for hospice care because of heart failure and reoccurring ischemia and severe end stage renal disease. He died on 10-8-13 with a presumption of a cardiac death. No autopsy or other confirmed diagnosis that this was the cause of death.

Summary: This was a 62 year-old man, enrolled into the treatment arm of the ALERTS Study, with known severe coronary artery disease, multiple risk factors, and with at least two prior MIs and a moderately reduced ejection fraction. He had numerous ischemic “alerts” prior to his death, but these were not acted upon for reasons that are not clear. He was deemed to have a terminal illness, resulting in the explant of the Guardian device, and a presumption of a cardiac death shortly thereafter.

Case 4- [redacted] **(Treatment)**

Review: The patient was a 53 year old male with significant cardiovascular risk factors and a TIMI risk score of greater than 3 with diabetes, hyperlipidemia, hypertension, and obesity, enrolled into the treatment arm of the ALERTS Study. He had severe coronary disease, and had undergone at least four stent procedures, with the most recent performed February 22, 2013. He was enrolled in the ALERTS Study on May 16, 2013 and was randomized to the treatment/alerting group. The IMD implant was on May 22, 2013 and was without complications. Following his most recent visit on October 25, 2013 the patient had a "see doctor" alert but did not want to call the doctor's office because he was not having symptoms. He went to dialysis that morning and was apparently not feeling ill. However, earlier in the week he had complained of chest pain but again did not call the doctor due to his symptoms. Three days later on October 27, 2013 the patient felt "hot and sweaty" while sleeping. The wife returned and found him unresponsive. The paramedics were called; CPR was performed, and the patient arrived in the ER in asystole without an ability to resuscitate the patient. No autopsy was performed. There was no device capture associated with the death event because the patient had already been buried and the device could not be retrieved. The patient had had some prior "see doctor" alarms due to elevated heart rate.

Summary: In summary, the patient is a middle aged gentleman with severe artery disease status post four prior coronary intervention procedures, with severe risk factors who had some chest pain and perhaps other symptoms preceding a cardiovascular arrest. Based upon the totality of the data it is not clear whether this could have been a primary arrhythmic death or possibly an acute MI. The event recordings could not be retrieved, as above. This should be deemed a cardiac death but not necessarily an ischemic/STEMI event. In other words, it is not clear that this was a false negative event. It is possible that this could have been a primary VT/VF arrhythmia (fatal arrhythmic event).