FDA Executive Summary

Prepared for the
March 16, 2016 meeting of the
Circulatory System Devices Panel

P150009
AngelMed Guardian System
Angel Medical Systems, Inc.

Introduction

This is the FDA Executive Summary for the AngelMed Guardian System. The AngelMed Guardian device is an implantable cardiac monitor intended to alert patients to ST segment shifts on the intracardiac electrogram indicating coronary ischemia. This device is intended for use in patients with prior acute coronary syndrome events, and in patients at risk for recurrent coronary events. Feasibility and Pivotal clinical studies were conducted between March 23, 2007 and January 13, 2014 under IDE G060259. The purpose of the IDE was to determine the device's effectiveness in detecting ischemic events and the safety of the implantable device. Angel Medical Systems, Inc. (the Sponsor) submitted a Premarket Approval Application (PMA) for marketing approval of the device (P150009) on February 19, 2015. This submission is being reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA's review to date of the PMA and its amendments highlighting the areas for which we are seeking your expertise and input. At the conclusion of your review and discussion of the data presented, FDA will ask for your recommendation regarding the benefit risk assessment for the device.

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1 PROPOSED INDICATIONS FOR USE

Angel Medical Systems has proposed the following indications for use for their proposed Device:

> *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.*

Angel Medical Systems proposes that the Guardian be indicated for the following patient population:

- Survivors of a previous Myocardial Infarction (STEMI or NSTEMI) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater.
- Patients with any prior ACS event also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater.
- Patients who have had or are scheduled for Coronary Bypass Surgery (CABG) also having one of the following, diabetes, renal insufficiency or a TIMI risk score of 3 or greater.

FDA Commentary 1:
The proposed Indications for Use (IFU) Statement above represents the most recent proposal from Angel Medical Systems. These proposed indications are based on the subjects enrolled and should be supported by the results of the ALERTS trial. The final Indications for Use, intended patient population and other labeling will be based on the completed analysis of the supporting data. Any comments offered by the Panel on appropriate supported indications will also be taken into consideration. .

2 DEVICE DESCRIPTION

2.1 Physical Device

The Guardian System consists of three main components which are shown in Figure 1 below and described in further detail below:

- Implantable Medical Device (IMD)
- External Device (EXD)
- A Programmer

Figure 1 Guardian System Component Diagram

2.1.1 Implantable Medical Device (IMD)

The IMD is implanted in a left pectoral subcutaneous pocket, similar to a permanent pacemaker, and connects to a transvenous active-fixation endocardial bipolar pacing lead which is placed in the right ventricular apex. Using a can-tip vector, the IMD monitors the intracardiac electrograms gathered in real time to assess for ST segment changes including ST depression and elevation. If the device detects an excessive ST shift relative to the baseline ST segment, and if the ST shift exceeds a pre-programmed threshold, the IMD vibrates to warn the patient and simultaneously signals the patient's external device (EXD) to provide redundant audible and visual external warning. The IMD also stores electrograms for subsequent retrieval by the Programmer via wireless telemetry.

2.1.2 Patient External Device (EXD)

The Patient EXD is a telemetry device given to each patient, which provides the redundant auditory and visual alerts via beeps and flashing LEDs when the IMD detects a cardiac event. The front of the EXD contains the Emergency and See Doctor indicator lights, and the Silence Alarm/Check Battery button. The back of the EXD contains a metal ring for attaching the neck cord if desired.

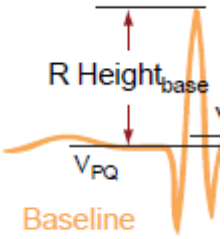
2.1.3 Programmer

The Programmer is a specially configured portable computer used to configure the IMD and retrieve and store IMD patient data, including electrograms collected by the IMD. The programmer uses an RF Telemetry interface through a Wand EXD to communicate with the IMD.

2.2 Device Functionality

The Guardian System's detection algorithm collects 10 second electrograms every 90 seconds (or 30 seconds if the previous segment was characterized as abnormal) and compares each against a running baseline that it develops from far-field electrograms (tip-can) it acquired over the previous 24 hour period. Specifically, it compares the ST deviation of each sampled beat to that of the baseline, and then compares that difference to the height of the baseline's R wave. (The ST deviation is the average voltage difference between a beat's ST and PQ segments.) These elements of the electrogram are shown in the figure below.

Figure 2 Detection Algorithm Visualization



If the difference exceeds the ischemia threshold established for the patient, which is a programmable and adjustable value, the beat is considered shifted. Within an electrogram, it takes six shifted beats to declare the electrogram shifted. If three consecutive shifted electrograms occur, the device records this as a detection of a possible ischemic event. The algorithm also tracks the heart rate by measuring the R-to-R interval and classifies the average heart rate of each electrogram as low, irregular, normal, elevated, or high. If the heart rate is low, normal, elevated or irregular, the electrogram will be assessed for ST segment shifts. If the calculated ST shift meets criteria, then the algorithm initiates an emergency vibratory and auditory alarm. If the heart rate is "high", then the electrogram will not be assessed for ST shifts. A "high" heart rate is defined by a programmable value and the default value is 160 bpm. In addition to the emergency alarm there is also a "See Doctor" alert which has a different auditory alarm and this alert can be triggered by high heart rates, low battery, or ST shifts specifically detected when the heart rate is abruptly decreasing, which the device presumes is exercise-induced ischemia due to increased demand and workload.

3 Regulatory History and Background Information

In 2005, based on successful GLP animal results, AngelMed initiated the CARDIOSAVER study in collaboration with the Dante Pazzanese Hospital of Cardiology in Sao Paulo, Brazil. The CARDIOSAVER study was designed to better understand the proper functioning of the Guardian system as it responds to an occlusion of a human coronary artery. The study included 20 subjects at high risk for heart attack, with the added indications that they:

- demonstrated ischemia on an exercise stress test,

- had an angiogram showing a stenosed coronary artery, and
- had a clinical indication for angioplasty and/or stenting.

The Guardian was implanted in these subjects with initial device programming performed shortly thereafter. Some of the subjects then underwent a repeat stress test with both intracardiac and surface ECG recordings used to assess ST segment changes with elevated heart rate. Next, each subject underwent PCI. The PCI procedures included balloon occlusion of the target artery. These occlusions lasted up to three minutes in order to provide intracardiac recording of ST segment changes associated with the resultant ischemia evoked by the balloon occlusion of the coronary artery.
In addition to this proof of concept, a number of significant improvements in the device and algorithm were made following the lessons learned in CARDIOSAVER.

In late 2006, AngelMed submitted an IDE (G060259) to the FDA requesting approval to begin a US based 20 subject safety study (the DETECT Clinical Study) with two primary objectives:

- Show that the AngelMed Guardian maintains a high safety profile when implanted in US patients
- Demonstrate that the Autopick function in the Physician Programmer would provide a reliable means for objectively selecting ST shift ischemia detection thresholds based upon statistical measures of each subject's normal daily range of ST segment variability

The DETECT study met its objective, demonstrating that the Autopick function provided greater specificity regarding ST shift detections.

The inclusion and exclusion criteria for the US DETECT study were different from those used in Brazilian CARDIOSAVER study. The DETECT subjects were survivors of a prior ACS event or bypass with additional risk factors that increased their probability of having a heart attack. DETECT was successful in showing that the IMDs could be implanted successfully and safely. Results from the DETECT and CARDIOSAVER studies provided the basis for the design of the ALERTS randomized prospective pivotal study with enrollment of 1020 subjects, conducted between 2008 and 2013. Multiple articles have been published describing the results from the CARDIOSAVER and DETECT studies in terms of the Guardian's ability to detect ST changes from coronary blockages including thrombotic occlusions from ruptured plaques.

The sponsor submitted two requests for pre-submission discussions related to the ALERTS clinical study prior to the modular PMA (M130018).

Q131440: The sponsor submitted this pre-submission request to discuss modifying primary and secondary effectiveness endpoints. This meeting included the multiple look-back windows, ensuring type 1 error is preserved for secondary effectiveness endpoints, changing some secondary effectiveness endpoints to "additional endpoints", and confirmation that FDA would look at the totality of the data when reviewing the PMA.

Q141014: The pre-submission focused on the new Q-wave MI dual baseline approach. During this meeting, FDA requested the PPV medical rules that ultimately were not submitted until S002 for this submission in January 2015. FDA expressed its initial disagreement with the new Q-wave MI approach that is further explained below.

4 NON-CLINICAL AND ANIMAL STUDIES

The sponsor has conducted characterization studies, animal studies and bench testing of the AngelMed Guardian System. The following information was provided, reviewed by FDA, and found to be acceptable.

- Test results demonstrating that the device is compliant with FDA recognized international standards for biocompatibility appropriate for this type of device.
- Test results demonstrating that the packaging and sterilization processes were validated according to FDA recognized international standards.
- Test results demonstrating that the device is compliant with FDA recognized international standards for electrical safety and electromagnetic compatibility.
- Complete software documentation, including test results from complete software verification and validation testing demonstrating acceptable performance.
- Test results demonstrating that the sensors maintain their mechanical and electrical integrity under conditions that simulate worse-case clinical use of the device.
- Data from animal studies which evaluate the device's *in vivo* functionality
- Complete human factors risk assessment of the proposed device

Please see the Sponsor's Summary of Safety and Effectiveness Data (SSED) for a more detailed description of the non-clinical testing conducted.

5 Overview of ALERTS Clinical Study and the Primary Effectiveness Endpoint

SUMMARY

This Overview section is intended to provide FDA's perspective on some of the data presented and the challenges that FDA had in interpreting the data in order to determine the device's effectiveness to detect acute ischemic events. Our intention is that it helps facilitate reading the Clinical study and Design section.

The Angel Med Guardian device was designed to detect intra-cardiac changes in the ST segment of the electrocardiogram as a means of detecting coronary ischemia. Although the ST and T wave changes that are seen on an electrocardiogram (ECG) have been well studied and characterized, the ST and T wave changes seen on the intracardiac electrogram are less well understood and have only been studied more recently [1, 2]. The Guardian device was studied under IDE to assess its ability to (1) detect ischemia and (2) detect an acute coronary occlusion, or an Acute Coronary Syndrome (ACS), and to (3) help get the patient to a medical facility in a timely manner by alarming and alerting the

patient to the ST detection. The primary effectiveness endpoint was a composite endpoint including (1) the time to present at a medical facility i.e. "time-to-door" for acute ischemic events or ACS events >2 hours, (2) new Q wave MI at 6 months, and (3) cardiac or unexplained mortality.

The ALERTS Clinical Study demonstrated that the AngelMed Guardian System met its primary safety endpoint. However, it didn't demonstrate the AngelMed Guardian system met the primary effective endpoints. The composite primary effectiveness endpoint presents some challenges in determining the device's effectiveness to detect acute ischemic events, particularly with respect to the time-to-door and the new Q wave MI endpoints. The quality of the ECG data and the inconsistency of the Q wave results caused the sponsor to terminate the study earlier than the protocol required, and to institute a dual baseline approach with serial reads to the ECG interpretation. The ECG data was not as clear or interpretable as anticipated when the trial was designed. The time to door endpoint was also less straightforward than originally anticipated in part because some of the qualifying events such as a positive stress test or disease progression by catheterization in the absence of acute thrombus or plaque rupture are more consistent with ongoing ischemia rather than an ACS event and therefore it is less intuitive what the time course for treatment should be. We acknowledge that FDA agreed with the trial design including the new Q wave MI and time to door endpoints but unfortunately over the course of the trial, and upon reviewing the results of the trial it has become apparent that there are inherent nuances and difficulties interpreting the results. We describe in this section the concerns and inconsistencies that were detected in each of the three components of the primary effectiveness endpoint, focusing mostly on the time-to-door and new Q wave MI components.

5.1 Time to Door >2 hours Endpoint

The time-to door endpoint was comprised of any patient that had a Guardian device detection of an ST shift followed by *any one* of the following testing results;

1) ECG showing ST elevation,
2) elevated cardiac enzymes,
3) a positive stress test showing ischemia, or
4) positive angiography.

A confirmed event was a guardian detection of an ST Shift (i.e., Emergency Alarm in the Treatment group or a data capture in the Control group) confirmed by any of the above four tests being positive or abnormal. However, having one of these tests be abnormal may be indicative of ischemia, but it may not necessarily be indicative of an ACS event, at least by Guidelines and Consensus Document definitions of ACS.

An ACS event is a broad term that indicates an acute ischemic event that warrants medical attention and includes unstable angina, non-ST-elevation Myocardial Infarction (NSTEMI), and ST Elevation Myocardial Infarction (STEMI). The main difference between unstable angina and NSTEMI is whether the cardiac biomarkers are positive for myocardial damage or not [3]. Both NSTEMI and STEMI, per the Expert Consensus

definition of MI, include positive cardiac biomarkers of which troponin I and Troponin T are the most commonly used [3]. In fact, their definition of MI includes positive biomarkers in addition to either symptoms or ECG changes, which include ST and T wave changes as well as new left bundle branch block (LBBB), or positive findings on coronary angiography.

The WHO definition of ACS and the 2011 Guidelines definition of unstable angina/ACS state that it is defined by ECG ST segment depression or prominent T wave inversion and/or positive biomarkers (e.g. troponin) in the absence of ST segment elevation and in an appropriate clinical setting such as chest discomfort.

Therefore, the criteria to diagnose a clinical ischemic event in the ALERTS trial were somewhat different than what is proposed by Guidelines and international definitions of MI or ACS. For example, a positive stress test for ischemia in the setting of negative cardiac biomarkers with a subsequent angiogram not demonstrating a plaque rupture or flow limiting lesion (typically >70% stenosis) meets one of the four pre-specified criteria for true positive ST detection in the ALERTS Study but is not considered an ACS by the ACC/AHA Guidelines. Similarly, an ECG showing ST depression or T wave changes in the absence of positive biomarkers or symptoms may represent ischemia but does not meet the definition of an ACS event.

This raises the difficulty of interpreting the Guardian device alarms and diagnosing possible ischemia, especially in the absence of symptoms in the instances where biomarkers were negative or the angiogram did not show a flow limiting lesion/plaque rupture. Although the criteria for MI and ACS have been well defined, the criteria for low level ischemia are less clear, especially if symptoms and/or cardiac biomarkers are absent or negative respectively.

In addition to the difficulty of determining the presence of ischemia even if ACS by Guidelines is not present, many of the subjects did not get the necessary testing to determine if ischemia or an ACS was present. In addition, there were many alarms (over 40%) that did not correlate to ischemia or an ACS and were classified as either Invalid or Inconclusive to be excluded from the analysis. Excluding 40% of the results is concerning since it is such a large percentage of the total alarms.

A third concern with the time to door calculation is that it assumes that the initial ST detection shift and alarm is the initiation of the ischemic event and should be treated as time zero. However, the data show some difficulties with this type of time-to-door analysis and raise the question of whether the ST shift correlates with the onset of ischemia. For example, there were 5 STEMIs during the course of the trial. Two of these ST detections were 47 minutes and 103 minutes respectively prior to presentation. However, two had an alarm 15 minutes and 13 hours respectively after the patient presented to the medical facility. And for one subject the alarm was 4 days prior to presentation at the medical facility. For the two subjects who presented prior to the ST shift detection, the ACS onset preceded the device detection. For the patient who had an alarm 4 days prior, although the patient may have had ischemia 4 days prior, it does not seem plausible that the STEMI began 4 days prior and was continuously ongoing.

Therefore, in the absence of subsequent alarms over the ensuing 4 days, it is difficult to know how to clinically apply that single alarm which occurred days before the STEMI began. Although the ST shifts may represent ischemia or correlate to STEMI events, the timing in these cases indicates that the device detection does not always represent the initiation of the acute event. Therefore, although the timestamp from the device accurately detects the onset of an ST shift it is not clear that it accurately reflects the true onset of the ischemic event or ACS.

Another aspect of the time-to door endpoint to be considered is how much time can lapse between the alarm and the event for them to be considered temporally correlated. The sponsor has calculated the time-to door for many time intervals between7 days through 90 days. Although 90 days allows a prior ischemic event to be detected at the per protocol visits which can be up to 3 months apart, it may be difficult to attribute an alarm to an event if there is a large gap in time between detection and medical intervention. One example is a subject who presented with symptoms, non-specific ECG changes and negative biomarkers and underwent PCI. The ST detection was 75 days prior and so the event counted as a >2 hour time to door event. Although the ST detection may have indicated ongoing ischemia in that subject, it is unclear how best to a correlate a specific ST detection on a given day with a clinical presentation that occurred months later. It is also unknown whether that subject would have had a better long term outcome if he/she had presented to a medical facility 75 days earlier than they did. How to apply the time-to-door paradigm in a case like this subject where there is no clear ACS event but the subject clearly had ongoing ischemia and warranted an invasive intervention is unclear. Treatment was warranted but it is not clear that it would have been preferable or necessary to take place within a few hours of the ST detection.

Another issue of concern to FDA is that the time-to-door endpoint should be calculated as the protocol specifies. The protocol states that positive test for ischemia is defined as any one of four positive test results (ECG, Enzyme, Stress and Angiograph) and ECG changes that are consistent with ST elevation should be included, not ST depression or T wave change. However, the sponsor included 4 control (alarm OFF) subjects with ST depression or T wave changes in the time-to-door > 2 hour calculation because it was felt that they had ongoing coronary ischemia. However, in these four subjects the other 3 tests which could have been used to corroborate the results were either negative or not done. In contrast, patients who had time-to-door >2 hours events in the treatment group had more than two positive tests for ischemia and therefore ECG change alone doesn't change the time-to-door >2 hours calculation in treatment group. When using a 90 day look back window for the time-to door endpoint and the dual baseline ECG approach, the posterior probability for the combined primary effectiveness endpoint was calculated to be 0.9908. However, when these 3 time-to-door events are removed from the analysis (3 ALARM OFF subjects) due to having ST depression rather than the protocol defined ECG changes of ST elevation without other positive testing (biomarker, stress test, or angiogram) to corroborate ischemia, the posterior probability is changed to 0.974. One of those 4 control subjects (b) (6) had both time-to-door >2 hours event and new Q wave MIs so he/she was not removed from the analysis. .

Lastly, it is unclear what the most appropriate manner to adjudicate an event is when a positive test is followed by a negative gold standard test. When using the four tests to determine an event (ECG, biomarkers, stress test, and angiogram) an ECG with ST elevation is considered a positive event. However, if the biomarkers are negative should it be considered an event? Similarly, if a stress test is positive for ischemia and the angiogram does not show obstructive coronary disease, should it be considered a positive event? The ALARM OFF group had one subject with only a positive stress test. A subsequent angiogram was negative for obstructive disease by the investigative site and the Core Lab. Since the subsequent angiogram was negative and no intervention was done, this positive stress test is considered by FDA to be removed from the analysis along with above 3 control subjects,, The posterior probability for the combined effectiveness endpoint is changed to 0.963. This calculation assumes a dual baseline ECG approach and 90-day maximum look-back window for later arrival.

5.2 New Q Wave Endpoint

A new Q wave seen in one or more ECG leads that was not present on the baseline ECG was counted as a new Q wave MI if there was no prior Q waves in a lead from the same zone or anatomic region. For example, if there were no Q waves in the inferior region (leads II, III, AVF) on the baseline ECG and then there was a Q wave in lead III at 6 months, it would be considered a new Q wave. Another example is that if the baseline ECG had a Q wave in lead III and then there were Q waves in leads II, III, AVF at 6 months it would not be counted as a new Q wave.

Per protocol, a new Q wave MI was a new Q wave in an anatomic zone that was present on the 6-month ECG where there were no Q waves present on the baseline ECG in that zone; the ECG was divided into inferior, anterior, lateral, and high lateral zones. The Core Lab used the criteria of 1 mm deep and 1mm in width for a pathologic Q wave. The protocol definition of a new Q wave MI differs from the Universal Definition published in the literature (see Table 1) [3] In general, the universal definition requires two contiguous leads in an anatomic distribution (inferior, anterior, lateral) to have Q waves except for a Q wave in V2 or V3 rather than a Q wave in any lead.

Table 1 ECG Changes Associated with Prior Myocardial Infarction per the Universal Definition of MI

- Any Q wave in leads V2-V3 >0.02 sec or QS complex in leads V2 and Vr
- Q wave $\geq$0.03 sec and $\geq$ 0.1mV deep or QS complex in leads I, II, aVL, aVF or V4-6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF)
- R wave $\geq$ 0.04 sec in V1-V2 and R/S>1 with a concordant positive T wave in absence of conduction defect.

One of the difficulties with using isolated Q waves is that they are known to come and go particularly in certain leads such as leads AVR and lead III [3] which can also have a Q wave as a normal variant. Q waves can also be seen in the absence of a prior MI due to incorrect lead placement, rotation of the heart, or severe emphysema [3]. During the course of the trial, the ECG Core Lab did find data quality issues regarding this endpoint because Q waves were seen coming and going, raising concern that they were not representative of a prior infarct since significant pathologic Q waves should be persistent.

This difficulty with interpreting the Q waves on ECG led to incorporating a change in the protocol regarding the interpretation of the ECGs. The ECG Core Lab re-read the ECGs but in a serial fashion per subject rather than in a random fashion to ensure that Q waves were only counted if they persisted. In addition, the Core Lab used an additional baseline ECG to ensure that any Q waves, or lack thereof, seen at baseline were consistent between the two baseline ECGs. Using two baseline ECGs (dual baseline approach) and reading the ECGs in a serial fashion for each subject allowed for ensuring that any Q wave seen at baseline had to be present on both ECGs and therefore more likely to be a "true" Q wave. New Q waves seen on the 6-month ECG may have also been present on the 3-month ECG or on both the 1-month and the 3-month ECGs. However, a Q wave first seen at the 6-month time point was not required to have a second ECG performed to ensure that it is a "true" Q wave. Additionally, the protocol did not require imaging to demonstrate a new wall motion abnormality in subjects diagnosed with an interval Q wave MI.

When the ECG protocol was changed by the ECG Core Lab, the interpretation of the baseline ECG in four subjects changed and this led to a reversal in their final result and these four subjects were no longer counted as having had a new Q wave MI. This resulted in the composite primary endpoint being changed from negative (posterior probability of 0.974) to positive (posterior probability of 0.9908). This is assuming a 90 day look back window and the significance threshold for the primary effectiveness endpoint was a posterior probability of 0.983.

5.3 The Reduction of Cardiac or unexplained Death Endpoint

There were very few deaths in the Alerts study; there were 3 deaths adjudicated as cardiac/unknown in the treatment (Alarm ON) arm and 1 death adjudicated as unknown in the control (Alarm OFF) arm (0.7% vs. 0.2%). This difference was not statistically significant. This endpoint is fairly straightforward and FDA does not have concerns with this component to the composite primary effectiveness endpoint.

6 CLINCIAL STUDY AND DESIGN

SUMMARY

- A total of 1020 subjects were enrolled in the ALERTS Clinical Study with 910 subjects actually implanted and 907 subjects both implanted and randomized (1:1) into Alerting ON (Treatment) or Alerting OFF (Control) groups. 451 Alerting ON (Treatment) group subjects had alerting enabled while 456 Alerting OFF (Control) group subjects had alerting disabled for six months (enabled at the six-month visit). The protocol required all subjects to have follow-up visits at one, three, and six months, then every six months from that point onward. ALERTS clinical study was designed as a Bayesian adaptive trial to allow multiple interim looks for sample size adjustments to ensure the study was adequately powered.

- The primary safety endpoint was to demonstrate a >90% rate of freedom from system-related complications.

- The primary effectiveness endpoint was a composite of late arrival (>2 hours) after a confirmed occlusive event, new Q-wave, and cardiac or unexplained death.

- Secondary effectiveness endpoints included components of the primary effectiveness composite, time-to-door analyzed continuously and other endpoints for patients at high risk for silent ischemia.

- Pre-specified thresholds of posterior probabilities were specified in order to determine statistical significance. Posterior probabilities are based on calculations assessing treatment superiority over 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 (determined by trial and error in the simulation to achieve a type I error rate that is at most 0.05)
    - Primary effectiveness endpoint significance threshold: 0.983 (determined by trial and error in the simulation to achieve the overall type I error of the design not exceed 0.025)
    - Secondary effectiveness endpoint significance thresholds: 0.975 (multiplicity adjustment was pre-specified in the protocol)
    - Significance thresholds for all other analyses were set at 0.975

6.1 Study Population

The study population includes subjects presenting with high-risk acute coronary syndromes or multi-vessel coronary artery bypass surgery as a result of coronary artery disease.

6.1.1 Inclusion/Exclusion Criteria

The ALERTS Clinical Study subject profile involved the following requirements:

- Advanced Multi-vessel Cardiac Disease
- An index ACS event (MI, Unstable Angina or CABG) within six months of subject enrollment.
- Additional risk factors/co-morbidities (diabetes, TIMI risk score ≥3, or renal insufficiency).

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.

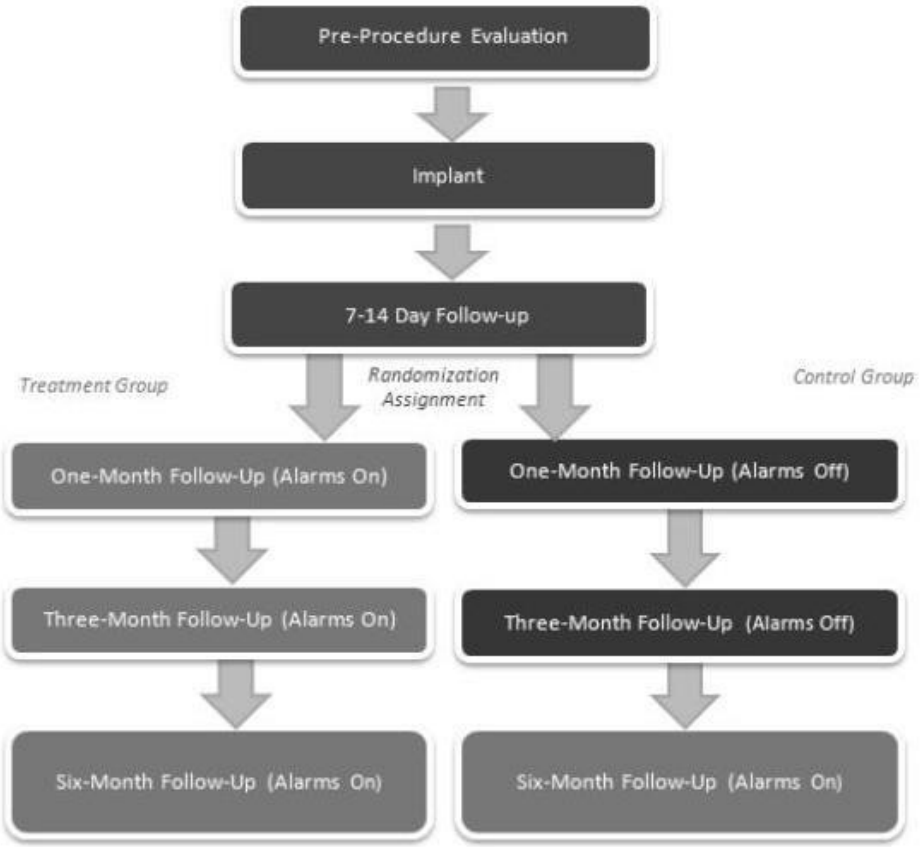
The full inclusion and exclusion criteria are provided in Appendix A.

6.2 Implantation, Randomization, and Treatment Protocol

A total of 1020 subjects were enrolled in the ALERTS Clinical Study with 910 subjects actually implanted and 907 subjects both implanted and randomized (1:1) into Alerting ON (Treatment) or Alerting OFF (Control) groups. Alerting ON (Treatment) group subjects had alerting enabled and were trained on how to recognize alerts and what actions to take as a result. Alerting OFF (Control) group subjects had alerting disabled for six months, and were told the device would not alert them. ST segment shift detections were recorded in the device and retrieved at protocol visits. For the Alerting OFF (Control) subjects, Guardian alerts were enabled at the six-month follow-up visit. Both Alerting ON (Treatment) and Alerting OFF (Control) groups were provided standard of care instruction on paying attention to the symptoms of a heart attack. Subjects (and their physicians) knew which group they were in. The protocol required all subjects to have follow-up visits at one, three, and six months, then every six months from that point onward.

Figure 3 shows the process followed for Alerting ON (Treatment) and Alerting OFF (Control) group subjects during the ALERTS Clinical Study. After enrollment but prior to the Guardian implant, a first baseline (12-lead) ECG was recorded (the "pre-implant ECG"). The Guardian IMD was implanted, using a procedure nearly identical to that of a single chamber pacemaker, requiring virtually no additional physician education on the implant procedure itself. A single IS-1 active fixation pacemaker lead was positioned and then fixed at or near the apex of subject'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. Any adverse events and complications were recorded.

Figure 3 ALERTS Clinical Study Process



Subjects were randomized 1:1 to the Alerting ON (Treatment) and Alerting OFF (Control) groups when they returned to the site for programming of the Guardian IMD 7-14 days after implantation. Both the Alerting ON (Treatment) group and Alerting OFF (Control) group subjects had ST shift detection enabled. However, only the Alerting ON (Treatment) group subjects had alerting turned on; the Alerting OFF (Control) subjects had alerting turned off. The randomization was stratified by site with a blocking scheme that consists of blocks of randomly varying size. A second baseline 12-lead surface ECG was also collected at the time of randomization (the "randomization ECG").

The protocol required all subjects to have follow-up visits at one, three, and six months, then every six months from that point onward. At each visit the subject's IMD event status was uploaded to the Physician Programmer for review. For the Alerting OFF (Control) subjects, Guardian alerts were enabled at the six-month follow-up visit, consistent with the parameters of the Alerting ON (Treatment) subjects' programming, which they received at 7-14 days post implant (i.e., at six-months the Alerting OFF (Control) subjects transitioned to "alerting on").

6.3 Event Definition

Table 2 provides a list of terms and definitions that were used in ALERTS.

Table 2 Event Definitions in ALERTS Study

Event	Definition
Occlusive Event	An Occlusive Event is defined as the detection by the AngelMed Guardian implant of an *ST Shift* that exceeds a pre-set patient specific *ST Shift Threshold* where the shifted beats have R-R intervals that correspond to a non-elevated "normal" heart rate range. Occlusive Events generate an Emergency Alarm with subject notification in ALERTS Clinical Study Treatment group subjects and a data capture, without subject notification, in ALERTS Clinical Study Control group subjects.
Positive Test/Positive Test for ischemia:	This is as defined in the ALERTS Clinical Study protocol to be one of the following: • ST elevation via 12-lead ECG as determined by blinded, independent Core Lab Review. • 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. • A Stress Test that was positive for ischemia. • Angiography (via independent angiographic CORE Lab analysis) showing any of the following: o A TIMI Flow Grade < 3 o A TIMI Frame Count > 40 o A TIMI Myocardial Perfusion Grade of 0 or 1 o New thrombus o New ulcer o Distal embolization o Dissection o New wall motion abnormality
Confirmed Event	A Confirmed Event is an Occlusive Event (as previously defined) that is confirmed to be "real ischemia" by a positive test for ischemia (as previously defined) **and adjudicated by the AGEA committee.** A Confirmed Event is used only for ALERTS Clinical Study endpoints where time-to-door is measured from the Guardian detection of an Occlusive Event to presentation at a medical facility where a Positive Test occurs.

Time-to-door for a confirmed event	As used in the primary and secondary endpoints of the ALERTS Clinical Study, this is 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 (as previously defined). • If the Time-to-door for a Confirmed Event is >2 hours it is called a Late Arrival Confirmed Event. • If the Time-to-door for a Confirmed Event is <2 hours it is called an Early Arrival Confirmed Event.
ACS Event or Confirmed Positive Event Alarm (CPA)	ACS event or confirmed positive event alarm (CPA) is a sponsor adjudicated event used for other endpoints, evaluation of positive predictive value (PPV) of an Emergency Alarm, and evaluation of the necessity of cardiac catheterizations. An ACS event is identified by one or more of the following indications: • A 12-lead ECG with ST Segment changes per either the 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 ** indicates the ACS Event criteria that differ from a Positive Test defined above
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).

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.
Control and Treatment Cohorts	These are the two groups into which ALERTS Clinical Study subjects were randomly assigned. Note these cohorts are sometimes identified by alternate terms for example: ALERTS ON/ALERTS OFF; ALERTING ON/ALERTING OFF; ON/OFF for Treatment/Control respectively in this document.

6.4 Endpoint Measurements, Adjudication, and Study Oversight

Primary and secondary effectiveness 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 effectiveness 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 effectiveness 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.

6.5 Primary Study Endpoints

6.5.1 Effectiveness

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

- Cardiac or unexplained death,
- New Q-Wave MI, determined as being a new Q wave in the six-month ECG that was not present before subject randomization, or
- Arrival at a medical facility for a confirmed thrombotic event more than two hours after detection of ST segment changes exceeding the detection threshold by the Guardian.

6.5.1.1 Statistical Analysis

At the 6-month follow-up visit, every subject will be counted as having had an event or not. Let R_t represent the rate of events in the treatment group (with Guardian alert activated) and R_c represent the rate of events in the control group (with Guardian alert inactive). Here, "rate" means the proportion of subjects who experience the event in 6 months. Of interest is the posterior probability π that the rate of events is lower in the treatment group; i.e., $\pi = Pr [R_t < R_c | data]$. A suitably high value of π will constitute evidence that the Guardian Alert reduces the event rate.

The event rates R_t and R_c will be assigned independent Beta(1,1) prior distributions. When all subjects have completed follow-up, the posterior distribution for R_t and R_c will therefore follow Beta(1+Et, 1+NEt) and Beta(1+Ec, 1+NEc) distributions, respectively, where E_t = the number of subjects with events in the treatment group, E_c = the number of subjects with events in the control group, NE_t = the number of subjects with No Event in the treatment group, and NE_c = the number of subjects with No Event in the control. The posterior probability $\pi = Pr[R_t < R_c | data]$ will be calculated from the distribution of the difference $(R_t – R_c)$.

6.5.1.2 Interim Analysis

When 600 subjects have been randomized, the predictive probability of eventual trial success (if subject accrual were to be stopped at this point) will be calculated. This probability is based on all available information; specifically, the patient's status (event, no event) will be known at 1 month and at 3 months, and this information will be utilized in the calculation of the predictive probability of eventual success. For subjects who have reached the 6-month follow-up visit, their final event status is known. For subjects who have reached the 1- or 3-month follow-up visit but not the 6-month visit, their final status will be imputed based on knowing the results of the 1-month or 3-month status (event, no event) and the observed, within trial correlation of events at these interim time points and at the 6-month time point. For subjects who have not yet reached 1 month, their final status will be imputed based on the experience of those patients who have reached the 6 month visit.

Let P_n denote this predictive probability of eventual success for the primary effectiveness objective, calculated when n subjects have been randomized. Let S_n and F_n be the Success

and Futility thresholds upon which the decision to stop subject accrual is made. Specifically, for n < 3000, if

- $P_n > S_n$, stop enrollment because eventual success is likely
- $P_n < F_n$, stop enrollment because eventual success is unlikely (futile)
- $F_n \leq P_n \leq S_n$, enroll another 300 subjects

The values of S_n and F_n that are selected for this design are shown in Table 3. The earliest that the trial could terminate for futility is when 1800 subjects had been randomized. The total number of "Sample Size" analyses can range from a minimum of 1 to a maximum of 8, and the total number of "Win" analyses can be 1 or 2.

Table 3 Thresholds for stopping accrual at each interim analysis (i.e., when *n* subjects have been accrued). F_n =threshold for futility. S_n = threshold for likely success.)

n	F_n	S_n
600	0.0	0.98
900	0.0	0.98
1200	0.0	0.98
1500	0.0	0.95
1800	0.0005	0.95
2100	0.001	0.90
2400	0.001	0.90
2700	0.005	0.85

6.5.1.3 Criteria for Success on the Primary Effectiveness Objective

At the conclusion of the trial, if the posterior probability π is greater than the cutoff Π_{Final}, the trial will be considered to have successfully demonstrated a reduction in the rate of events (i.e., R_t is statistically less than R_c). When the accrual of subjects is stopped, an Early Win will be declared if the predictive probability of eventual success P_n is greater than the cutoff $\Pi_{Interim}$. However, no Early Win analysis will occur if accrual stops at 600 enrollments. In symbols, a reduction in event rates will have been established if

- $P_n > \Pi_{Interim}$ (immediately after accrual has stopped, provided that $n \geq 900$ and n/2 subjects have completed 6 months follow-up); or
- $\pi > \Pi_{Final}$ (at the final analysis, when all randomized subjects have reached 6 months)

The following cutoff values are selected for this design:

$$\Pi_{Interim} = 0.995$$
$$\Pi_{Final} = 0.983$$

The values $\Pi_{Interim}$ and Π_{Final} are determined by trial and error and are chosen so that the design's operating characteristics under simulation are acceptable. Specifically, it is important that the overall type I error of the design not exceed 0.025. It is also the desire of the sponsor to have at least 80% power to detect a reduction in event rates from 4% to 2% as well as the opportunity to stop accrual early if the event rates are higher.

6.5.2 Safety

The primary safety analysis was to determine whether the proportion of subjects free of system-related complications (denoted as p) is >90%, at six months (i.e. the incidence of system-related complications is < 10%) for all implanted patients. The protocol defines a system-related complication as any adverse event related to a successfully implanted system that requires a system revision (invasive intervention) to resolve.

The acceptance criteria for primary safety endpoint is $P(p>0.9| data) > 0.954$, which was found by trial and error in the simulation to achieve a type I error rate that is at most 0.05, under all realistic enrollment patterns and correlation scenarios.

6.6 Secondary Endpoints

While there are many pre-specified secondary objectives in the ALERTS clinical study, only the first six are designated as objectives for which FDA-approved labeling claims may be sought and multiplicity adjustment was pre-specified on those six secondary endpoints. The rest of the secondary objectives have been pre-specified but are intended to be exploratory and supportive in nature, and not the basis of specific labeling claims. Of these six secondary endpoints, 3 were the individual components of the primary effectiveness 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 effectiveness 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

6.7 Other Endpoints

The ALERTS Clinical Study protocol also included a number of additional pre-specified endpoints as "Other Endpoints". Those endpoints have been summarized in the table provided in Appendix C to this document.

7 Study Conduct – Protocol Deviations and Modifications

SUMMARY

- The ALERTS clinical study was terminated early due to concerns of incomplete and unreliable data. However, the decision of enrollment termination is viewed as a significant protocol violation. Ideally, the conduct of the trial should follow the pre-specified study design. Terminating the trial in this unplanned fashion may undermine the validity of the trial from a compliance and integrity perspective and make the interpretation of data challenging.
- The use of "dual baseline" ECG interpretation was proposed to address possible ECG inconsistencies seen on the baseline ECGs after the sponsor reviewed the data. The "dual baseline" post-hoc analysis which was performed after the final effectiveness analysis could overestimate the treatment effect. In addition, FDA believes that there are likely to be similar reliability issues with ECGs done at 1, 3, and 6 months which could impact the accuracy of the new Q wave MI endpoint.
- Multiple look-back windows ranging from 7 days to 90 days were proposed for the maximum allowable time between ST shift detection and the "late arrival" for a "confirmed occlusive event. No multiplicity adjustment was planned or conducted in the primary effectiveness analysis across different look-back windows. Neglecting multiplicity could lead to false declaration of significance and therefore spurious inference.
- There were 4 control subjects who presented with ECG changes. These changes were ST depressions and T wave changes rather than ST elevation and therefore do not meet the per protocol AGEA definition for a positive standard of care test. However, they were included in the primary and secondary endpoint analyses by the sponsor as positive clinical events.

During the course of the ALERTS study, the sponsor made two adjustments in study conduct which FDA considers major study protocol deviations. The first adjustment the sponsor made was to stop the trial early as the sponsor was concerned about the interim data quality (7.1). The second adjustment was related to improving the reliability of the ECG reference baseline data by using a dual baseline ECG analysis (7.2).

In addition, there were two other protocol changes made during the course of the study. First, the sponsor initially requested that the look-back window be 7 days for the primary effectiveness endpoints. Then in 2013 they requested that the look back window be lengthened to 90 days (7.3). The protocol changes for look back windows were conducted while the sponsor was blinded. Secondly, a Positive Predictive Value (PPV) calculation was requested by FDA in 2014 to demonstrate diagnostic performance of the Guardian System (7.4).

7.1 Early Termination of Clinical Studies (Protocol Violation)

The ALERTS trial was designed to prospectively enroll patients, but rather than have a pre-determined enrollment goal based on an a priori power calculation and assumptions made on event rates (frequentist approach), the study was designed as a Bayesian adaptive trial which allows for multiple interim looks to assess the need for sample size adjustments and to ensure that the study is adequately powered. The original sampling plan for the ALERTS Clinical Study involved potential interim analyses at each of the following sample sizes: 600, 900, 1200, 1500, 1800, 2100, 2400, 2700, and, if necessary, 3000. However, only interim looks at N=600 and N=900 were done. The interim analyses at 600 subjects and at 900 subjects both indicated that enrollment should continue. However, Angel Medical subsequently realized that the interim data were unreliable and decided to stop enrollment at the N=900 interim analysis. The sponsor believed that unreliable interim data were caused by an incorrect assumption they made in the trial design, incomplete and invalid data entry, and reporting delays. Specifically, regarding the New Q wave component of the primary composite endpoint, the premise that a new Q-Wave in a one- or three-month visit ECG identified by the Core Lab would predict with certainty the presence of the new Q-Wave at six months was not true. In addition, the data used in the early interim analyses were often incomplete and in some cases incorrectly entered in the study database (both issues subsequently remedied through the monitoring process). Therefore, the sponsor believed that the predictive aspect that was specified in the design was neither accurate nor supportable, and they felt that ceasing new enrollment and performing analyses on the available data was the best way forward. Given that FDA had agreed to a trial expansion up to 1020 subjects in order to continue enrollment during the interim look at 900 subjects, the sponsor decided to stop new enrollment after the 1020 enrollments had been reached. The final analysis was conducted once all randomized subjects had passed 6 months and their final outcomes could be ascertained. The final size of the randomized cohort was 907 subjects.

The difficulty with this change in the protocol is that the operating characteristics of the ALERTS trial and the control of type I error were all based on the pre-specified study design in the protocol using multiple interim looks. Since the sponsor failed to follow the protocol, the validity of the trial may be undermined from a compliance, data quality and trial integrity perspective; which in turn may compromise the Bayesian inferences on the primary and secondary endpoints.

FDA Commentary 2:
Although FDA agreed to expand enrollment to 1020 subjects in order to cover the planned interim look at N=900, FDA did not agree to stopping the trial early. The interim looks showed that the trial should continue. The sponsor's decision to terminate enrollment early is considered a major protocol violation, which may undermine the validity of the trial from a compliance and integrity perspective *and makes the interpretation of the trial data challenging.*

7.2 Dual Baseline

In the pre-approved study protocol, a single baseline ECG at randomization was used to define a "New Q-Wave MI". Since it is expected that a new Q wave will persist, only patterns of no Q wave present in a given lead to a new Q wave present in that lead were

accepted to meet the endpoint of new (pathological) Q wave MIs. These patterns were assessed in the four ECGs collected respectively at randomization, one, three, and six months as shown in Table 4.

Table 4 Q-Wave Patterns to Qualify for "New Q-Wave MI" with a Single Baseline

Baseline at Randomization	1 Month Visit	3 Month Visit	6 Month Visit
Absent	Present	Present	Present
Absent	Absent	Present	Present
Absent	Absent	Absent	Present

During the course of the ALERTS Clinical Study, the sponsor detected that an assumption made in the design of the study related to the presence of "pathological" Q waves (i.e. those resulting from an infarction of cardiac muscle) was not completely valid in a "real world" context. That assumption 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 Clinical Study, that quality control factors could cause a Q wave to appear in the ECG at one subject visit and then subsequently to disappear at a later subject visit. These quality control issues were related to real world issues such as inconsistent or improper electrode placement or noise in the signal. Therefore, the sponsor was concerned that the Q wave may not have been detected accurately in the single baseline ECG that was then used for the comparison to the six-month ECG. Since the protocol required that pre-implant ECGs be collected for all subjects, AngelMed proposed to use a "dual baseline" (pre-implant ECG and the randomization ECG) for an additional analysis and FDA emphasized that the "dual baseline" analyses can only be counted as post-hoc analyses.

Table 5 Q-Wave Patterns to Qualify for "New Q-Wave MI" with Dual Baselines

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

FDA Commentary 3:
FDA is concerned that use of the dual baseline was proposed after the sponsor saw the data and the final analysis was performed. Even though the ECG Core Lab was still blinded to treatment group when the ECGs were serially re-read for individual subjects, this post-hoc analysis after the final analysis was performed could overestimate the treatment effect.

In addition, FDA has concerns with the quality and reliability of the data collected and the interpreted results. If there were reliability issues with the baseline ECGs in which Q waves did not persist on serial ECGs and therefore were not indicative of a prior MI, there are likely similar reliability issues with ECGs done at 1,3, and 6 months. For example, if a new single Q wave was present at the 6 month visit only, there is no subsequent ECG to assess whether the Q wave remained or resolved. Although multiple serial ECGs showing the same Q waves can be reassuring that they are representative of a prior MI, if only the 6 month ECG shows a Q wave, it is difficult to know how reliable it is given the baseline ECG difficulties or how indicative it is of an interval MI.

7.3 Look-back window

The "time to door" for a confirmed thrombotic event was measured from the (first) time the Guardian detected an ST-shift event to the time of first presentation at a medical facility where testing revealed a positive test for ischemia (either ST elevation on ECG, positive biomarkers, a positive stress test, or a positive angiogram) which is termed "a confirmed thrombotic occlusive event" by the sponsor. Since the original ALERTS statistical analysis plan (SAP) approved by FDA in 2008 did not specify a maximum allowable time between ST shift detection and the "late arrival" for a "confirmed occlusive event", the sponsor initially requested that the look-back window be 7 days.

However, the sponsor was developing an understanding of the behavior of silent ischemic subjects; realizing that in the absence of symptoms or when symptoms are ignored or misunderstood, a subject might never present emergently, and that the evidence of the cardiac event would only be (potentially) detected at a regularly scheduled visit. Therefore, the sponsor requested that the look back window be lengthened to 90 days from 7 days as 90 days is the maximum time between the 3-month and 6-month follow-up. SAP was amended in 2013. Please note that look-back windows only apply to patients in the Alerting OFF (Control) group.

Empirical support for the relevance of the 90-day look-back period is seen in Table 6, which presents counts of events according to duration of delay in arrival, using a maximal look-back period of 90 days.

Table 6 Time to Arrival for subjects with confirmed thrombotic occlusive events

Time to Arrival*	Alerting ON Group	Alerting OFF Group
< 2 hrs	29	1
2-6 hrs	1	0**
6-24 hrs	3	0***
24-48 hrs	1	2
2-7 days	0	3
8-30 days	0	6
31-50 days	0	2
51-70 days	0	2
71-90 days	0	2

*** from first detection in 90-day look-back window to presentation for confirmed event**
**** Two subjects with a detection > 20 days prior to arrival also had a subsequent detection within this period**
***** One subject with a detection > 20 days prior to arrival also had a subsequent detection within this period**

FDA Commentary 4:
No multiplicity adjustment was planned or conducted in the primary effectiveness analysis across different look-back windows. Multiplicity issues could inflate the type I error rate if not handled correctly. Neglecting multiplicity could lead to a false declaration of significance and therefore spurious inference.

7.4 PPV Calculation

The FDA pointed out at the ALERTS review meeting in June 2014 that an analysis of sensitivity and specificity would be inappropriate for the ALERTS data. The sensitivity and specificity can be calculated when the **known** disease status is to be detected by the test device. However, the disease status was unknown in the ALERTS study and alarms were detected by the test device first, then confirmed by one of four clinical reference methods (ECG, stress test, biomarkers, and angiogram). Therefore, FDA recommended a calculation of Positive Predictive Value (PPV) related to Guardian alarms. The FDA and sponsor agreed that the PPV should only be calculated on the Alerting ON (Treatment) group for events that occurred during the randomization period. Additionally, the FDA and sponsor agreed that calculations involving false negatives and true negatives are unsuitable and should not be conducted because one cannot determine true and false negative disease status for Alerting OFF (Control) patients or Alerting ON (Treatment) patients who do not present due to an alarm.

The formula for calculating PPV is CPA/(CPA+NCPA) either as a fraction or a percentage, where CPA and NCPA are defined in Table 2.

Two classes of Emergency alarms are excluded from the PPV analysis:

– Inconclusive events - Emergency alarm events for which the protocol-specified standard of care tests were not performed by the site (for any reason, since this is not-compliant with the ALERTS Clinical Study protocol) or where there was incomplete/insufficient data for the Emergency alarm (data missing) so that it was excluded from the analysis.

– Invalid events – (a) Emergency alarm events where the Emergency alarm occurred while the subject was already present at a medical facility (inpatient, during medical procedure, or subject visit for alarm training) or (b) Emergency alarms caused by an algorithm anomaly that was subsequently eliminated by an improvement to the Guardian system during the study (such as the Recovery Event See Doctor alert – created to cover demand ischemia situations) or (c) Emergency alarms that occurred as a result of a programming error (and that type of programming error was eliminated by subsequent improvements in the current version of the Guardian System, during the course of the ALERTS Clinical Study).

8 STUDY RESULTS

SUMMARY

- The primary safety endpoint was met with a 96.7% event-free rate. The posterior probability of >90% of subjects free of system-related complications was >0.9999.

- The primary effectiveness endpoint, a composite endpoint including cardiac/unexplained death, new Q wave MI, and time-to-door > 2 hours, was not met:
  - Cardiac or unexplained death: Control group (1) and Treatment group (3)
  - New Q Wave MI: Control Group (14) and Treatment Group (10)
  - Time-to-door > 2 hours: 8 when using the 7-day look-back window or 17 when using the 90-day look-back window in the Control Group and 4 in the treatment group

  Using the 7-day look back window, the posterior probability of event reduction was 0.7856 (event rate: 3.8% Treatment vs. 4.9% Control). Using the 90-day look-back window, the posterior probability of event reduction was 0.9740 (event rate: 3.8% Treatment vs. 6.8% Control). None of the posterior probabilities met the threshold for statistical significance, which is pre-specified as 0.983. These both incorporate the per protocol single baseline ECG Analysis.

- "Dual-baseline" post-hoc ECG Analysis:

  After unblinding, the sponsor proposed using a "dual-baseline" analysis to address the possible ECG artifacts at baseline. This changed the result in 4 subjects (3 Treatment and 1 Control) from having had a New Q Wave MI to no New Q Wave. Therefore these 4 results were not counted towards the New Q wave MI endpoint analysis. Using the "dual-baseline" analysis with a 90-day maximum look-back window for late arrival, the posterior probability of event reduction was 0.9908 (>0.983) (event rate: 3.1% Treatment vs. 6.5% Control). Although it surpassed the threshold of 0.983, the treatment effect or positive result could be overestimated due to the use of the "dual-baseline" since this analysis was done post-hoc after the ECG data was reviewed.

- Time-to-door events

  There were 4 control subjects who presented with ECG changes that consisted of ST depressions and T wave changes rather than ST elevation and therefore do not meet the AGEA definition for a positive standard of care test. Therefore these 4 subjects are no longer considered by FDA to have had an AGEA identified confirmed time-to-door positive event. After removing 3 of these 4 control subjects in the composite endpoint (One of the 4 subjects was not removed from the analysis since this subject had both a time-to-door >2 hours event and new Q wave MI), the "dual baseline" post-hoc analysis using the 90-day maximum look-back window for late arrivals didn't show Treatment group superiority (posterior probability=0.974 which is below the 0.983 threshold; event rates: 3.1% Treatment vs. 5.8% Control)

  In addition, 1 control subject presented with a positive stress test but a negative angiograph result which makes unclear whether this subject is considered as having a positive event. With 4 subjects (3 subjects with above ECG results and this subject) not considered by FDA to have had a confirmed time-to-door positive event in the composite endpoint, the "dual baseline" post-hoc analysis using the 90-day maximum look-back window for late arrivals didn't show Treatment group superiority (posterior probability=0.963 which is below the 0.983 threshold; event rates: 3.1% Treatment vs. 5.6% Control).

8.1 Baseline Demographics and Disposition

A total of 1020 subjects were enrolled in the ALERTS Clinical Study with 910 subjects actually implanted and 907 subjects both implanted and randomized. A breakdown of various demographic and historical characteristics for the randomized cohort, by randomized Alerting ON (Treatment) group, along with 95% Bayesian Credible Intervals (BCIs) for the between-group difference in means or proportions, as appropriate, is presented in Appendix B. A 95% BCI range that excludes 0 (such as 1.2%, 4.5%) indicates a statistically significant difference between the groups for that specific characteristic. Baseline characteristics are well balanced between Alerting ON (Treatment) and Alerting OFF (Control) groups. A few characteristics were statistically significantly different, but these are single categories of a multi-category characteristic, and when viewed as a multi-category response, they do not represent true statistical differences.

The mean age was 60 years and men comprised 68% of the total cohort. Caucasian ethnicity was the overwhelming majority of subjects enrolled (86%). Many subjects had a history of STEMI (24%), NSTEMI (28%) or unstable angina (44%). Approximately 6% had a history of silent MI but almost all had some form of angina in the 6 months preceding enrollment (88%). The mean LVEF was low-normal at 54%. Almost half the subjects had diabetes mellitus and almost all (>90%) had both dyslipidemia and hypertension. The population cohort therefore was enriched in order to capture more ischemic events and test the functionality of the algorithm. As stated above, the control and treatment arms were well matched; there were slightly more treatment arm subjects

with no prior history of silent ischemic changes and the control group had more unknowns for this category.

8.2 Safety Results

A total of 910 subjects were implanted with the Guardian with 895 having sufficient follow-up for the endpoint. There were a total of 364 Adverse Events (AE) which occurred in 271 subjects (129 control, 136 treatment, and 6 non-randomized); There were 31 system-related complication events in 30 subjects (3.3%) as defined for the primary safety endpoint. All adverse events were adjudicated by an independent Adverse Event Adjudication Committee. A breakdown of the causes of the 31 events in those 30 subjects is shown in Table 7. Infection was the most common AE with 11 subjects (1.2%). The infection rate was increased, in part, due to a failure to follow protocol at some study sites. Improper post-operative follow-up care (subject not following instructions) caused three infections, and defective air handling in one cath lab caused another. The Subjects column counts any subject who had the complication with one of the subjects showing up twice. The sponsor conducted the statistical analysis showing a posterior probability of the proportion of subjects free of system-related complications is greater than 90% giving 6 months study data shown as $P(p>0.9|data)$ was greater than 0.9999, which was used to support their claim the primary safety endpoint was met.

Table 7 Primary Safety Events (through 6 months, Including Sponsor-Identified Events and Events on Day of Implant

	All Subjects with Successful Implant (N = 910)			
	Events	**Subjects**	**%***	**95% BCI**
Cardiac Perforation	2	2	0.2	(0.1, 0.8)
Erosion**	2	2	0.2	(0.1, 0.8)
Infection	11	11	1.2	(0.7, 2.2)
Lead migration/dislodgement***	4	4	0.4	(0.2, 1.1)
Loss of sensing due to dislodgement or malfunction of the lead	2	2	0.2	(0.1, 0.8)
Pain at or near the pocket site	4	4	0.4	(0.2, 1.1)
System-related complication	5	5	0.5	(0.2, 1.3)
Visible bump where implanted in the chest	1	1	0.1	(0.0, 0.6)
Total	31	30****	3.3	(2.3, 4.7)

*** Percentage in # subjects experiencing event/# subjects with successful implant (x100)**
**** Includes 1 additional sponsor identified event**
***** Includes 2 additional sponsor identified events**
****** One subject experienced two different events and appears in two rows; the Subjects Total is the number of unique subjects in the column, and not the sum of the column entires**

8.3 Effectiveness Results

The objective was to determine the effectiveness of the Guardian device to detect a coronary occlusive event. The primary endpoint was comprised of the three following components; (1) cardiac or unexplained death, (2) new Q wave MI detected on ECG, and (3) time to door > 2 hours (time from Guardian detection of an ST shift to patient's time of presentation) for a confirmed positive standard of care test which the sponsor terms "thrombotic coronary occlusive event." The Time to door > 2 hours was only calculated for subjects who had a positive standard of care test which includes: (1) ECG with ST elevation, (2) elevated biomarkers, (3) a stress test that is positive for ischemia, or (4)

positive angiography per Core Lab that shows either TIMI flow <3, a new thrombus or ulcer, a dissection, or a new wall motion abnormality. Of note, if a subject experienced an alarm and presented to a medical facility but none of these four time-to-door tests were done, then the event was not counted towards the time to door endpoint or towards the primary effectiveness endpoint. The standard of care testing that was performed after an ST shift detection occurred was reviewed by an independent AGEA committee. A ST segment shift detection or alarm was termed "an occlusive event" by the sponsor and will be called "occlusive event" throughout the Results section.

8.3.1 Per-protocol Analysis of the Primary Effectiveness Endpoint

The ALERTS study was a randomized prospective clinical trial that was designed to determine whether the Guardian device reduces the composite endpoint of cardiac or unexplained death, presence of new Q wave MI at the end of the 6 month follow up period, and the incidence of time-to-door presentation greater than 2 hours.

The composite primary effectiveness endpoint and the posterior probability of coronary event reduction were computed.

8.3.1.1 Cardiac or Unexplained Death

During the six month follow up period there were a total of 6 deaths; 4 of which were adjudicated as either of cardiac origin or unexplained. There were 3 cardiac/unexplained deaths in the Alert ON (Treatment) group and 1 cardiac/unexplained death in the Alert OFF (Control) group. Each death was reviewed by the adjudication committee to determine whether it was due to a cardiac, unknown or non-cardiac cause. The three deaths in the alarm ON group were felt to be due to cardiac causes (0.7%). The etiologies of these deaths were attributed to "MI", "CAD", and "cardiorespiratory event". Device capture was not available for these three subjects. One of the 3 deaths in the Control group, 1 was felt to be due to an unknown cause since the subject was found pulseless (0.2%).

Table 8 Incidence of cardiac or unexplained death

	Alerting OFF Group (N=456)		Alerting ON Group (N=451)	
	n	Pts (%)	n	Pts (%)
Cardiac or Unexplained Death	447	1 (0.2%)	441	3 (0.7%)

Overall, the 6-month mortality rate was low for both groups. Statistically, this component did not drive the primary endpoint results. There does not appear to be a reduction in mortality from the Guardian device, however, there are insufficient data in the ALERTS study to make a conclusion on whether the Guardian System has an impact on mortality.

8.3.1.2 New Q-Wave MI detected on ECG

All subjects underwent a baseline ECG at the time of randomization and then a subsequent ECG was performed at 1, 3 and 6 months. The de-identified ECGs were sent to a Core ECG Lab at Duke University and the ECG readers were blinded to the subject and to the treatment arm. The randomization ECG and the 6 month ECG were then compared to each other to determine if there was a new Q wave on the 12 lead ECG that

was not present on the baseline 12 lead ECG. Of note, a single new Q wave in any lead was needed to meet this endpoint. This differs from the ACC/ESC accepted definition of a pathologic Q wave as:

- any Q wave in leads V2-V3 ≥0.02 sec or a QS complex in leads V2 and Vr
- Q wave ≥0.03 sec and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a continuous lead grouping (I, aVL; V1-V6; II, III, AVF).
- R wave ≥ 0.04 sec in V1-V2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect.

This method of including single Q waves was felt to be a more sensitive approach to detect interval ECG changes and better include infarctions that may have occurred during the study duration which were an extension of a prior infarct.

However, during the course of the trial, it was noted that Q waves on ECGs might not be present on a subsequent ECG. This led to a serial over-read of the ECGs, which included the baseline ECG and the 1, 3, and 6 month ECGs. This is further described below in section 8.3.2.1.

Only patterns of "absent Q" to "present Q" were included for this analysis as shown in Table 4 above. Shown here in Figure 4 and Figure 5 is an example of serial ECGs in a subject that was considered to have demonstrated a new Q wave MI using the criteria of presence of a new Q wave. Only the inferior leads are shown for this subject since the new Q wave (MI) was felt to be in the inferior distribution.

Figure 4 ECG at baseline

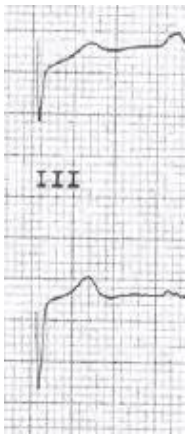
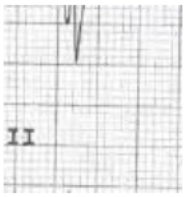


Figure 5 ECG at 6 months



This resulted in 14 control subjects with a new Q wave (3.3%) and 10 treatment subjects with a new Q wave (2.4%) as shown in Table 9.

Table 9 Incidence of new Q wave MI

	Alerting OFF Group (N=456)		Alerting ON Group (N=451)	
	n	Pts (%)	n	Pts (%)
New Q wave MI	427	14 (3.3%)	420	10 (2.4%)

There were 60 subjects that were unable to have this component of the endpoint determined due to the 6-month ECG being out of window (n=21) or having the device explanted prior to the 6 months (n=16), or death (n=6), no 6-month ECG performed (n=5), or the ECG being uninterpretable (n=10), other (n=2).

8.3.1.3 Time to door > 2 hours

When a patient is experiencing an ACS event, particularly a NSTEMI or STEMI, timeliness to seeking medical attention could potentially save cardiac muscle. If there is a coronary artery that is acutely occluded, the faster it is opened, the better the long term outcome for the patient. The 2013 ACCF/AHA Guidelines recommend that a patient with an ongoing STEMI have a door-to-balloon time of </= 90 minutes [4]. However, the purpose of this is somewhat defeated if the patient does not present or make it "to the door" of the medical facility for several hours. Therefore, the time to door endpoint for the ALERTS study was to demonstrate the device's ability to get patients to the medical facility in less than 2 hours when having an ACS. The device does this by alarming and signaling to the patient to seek medical attention. Of note, this endpoint assumes that the device accurately determines that ischemia is present and when the ischemic event began since the time to door calculation is based off of the alarm time stamp.

If there was an ST shift that exceeded the programmed threshold, this was classified as an "Occlusive Event". The time from alarm (treatment group) or detection (control group) to

presentation to a medical facility was calculated for all subjects with an Occlusive Event. The “time-to-door” was measured from the first time the Guardian detected an ST-shift event to the time of first presentation at a medical facility where one of four standard of care tests had a positive result. The standard of care testing included; ST elevation on ECG, or positive enzymes, or stress test showing ischemia or left heart catheterization being positive per the Core Lab. If the Occlusive Event, or ST shift detection, was followed by a positive standard of care test, it was classified as a “Confirmed Event”. (Also please refer to section 6.3 for more detailed definitions of the terms used.)

For subjects in the treatment group, the time to door was calculated from the timestamp of the alarm to presentation. For the control group, time was calculated from time of presentation where an event was confirmed by a positive standard of care test (any of the 4 standard of care tests) back to the first Guardian alert capture within the look back window. Patients in the control group presented mostly either for a protocol required visit or for symptoms. Of note, only one of the 4 tests had to be positive to be counted towards this endpoint. For example, if a subject had a positive ECG but negative biomarkers and no other testing was done, this was included in the time to door event analysis and adjudicated by AGEA as a Confirmed Event. Only AGEA adjudicated Confirmed Events were included in this calculation.

The time to presentation for a Confirmed Event looking back to the Guardian detection is termed the "look-back" window. Although the patients with the alarm on were able to respond to the alarm, patients in the control group only presented either for symptoms of possible cardiac ischemia or other complaints or for routine follow up visits per protocol. Therefore, the time to door could be much more variable and more difficult to adjudicate. The original SAP did not specify a maximum allowable time between ST shift detection and a positive standard of care test for control subjects. However, when this was identified, FDA and the sponsor discussed the issue and an IDE Supplement specified that the time cut off between symptoms or positive cardiac test and a preceding Guardian detection is 7 days. Subsequently, prior to completing the 6 month follow up for most subjects, this issue was revisited due to concern that control subjects with asymptomatic ischemic events may not present until a routine follow up visit. The sponsor requested that the look back window be lengthened to 90 days to account for the longest time in between protocol required follow up visits.

The ALERTS Clinical Study was amended to pre-specify analyses that included several look-back periods ranging from 7 days up to 90 days, to be evaluated as part of the totality of the evidence related to the primary endpoint.

Therefore, the results have been calculated using several time-to-door look back windows varying between 7 days and 90 days. As an example, if a control subject had positive enzymes and a positive ECG and the Guardian device showed a detection 30 days prior, this would not be included in the 7 day look back analysis but would be included in the 90 days look back analysis.

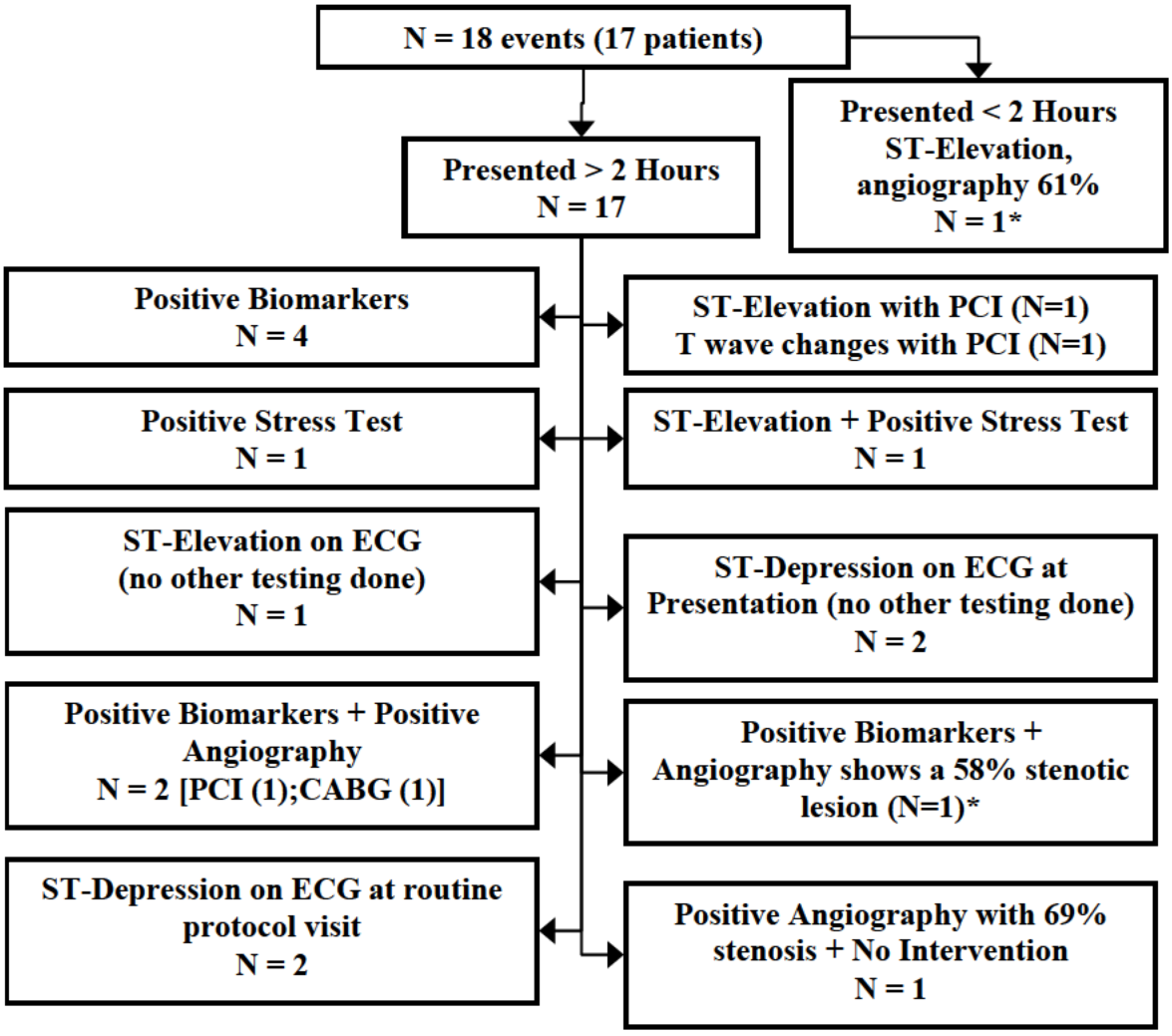
When using a look back window of 90 days, there were 17 control subjects who presented > 2 hours from time of Guardian ST shift detection and 1 of these control

subjects also presented within 2 hours of an ST shift detection for a total of 18 events. These 18 events constitute the control group's time-to-door events. Figure 6 also shows the breakdown of these 18 events.

For the 18 events that met criteria for a ST segment shift and a per protocol clinical ischemic event, they met criteria by the following,

- 3 underwent PCI
- 1 had positive biomarkers and underwent CABG
- 2 had stenosis by angiogram 58-69% with no intervention performed*
- 4 had ST depression on ECG only
- 2 had ST Elevation on ECG in absence of positive enzymes or angiogram at that time. One of these had a subsequent positive stress test.
- 4 had positive biomarkers only
- 1 had a positive stress test only. A subsequent angiogram at a later date was negative for obstructive CAD
- 1 had ST elevation and angiogram showed 61% lesion by Core Lab with no intervention* (presented < 2 hours)

Figure 6 Control Subjects Included in Time-to-Door Analysis



To summarize the time to door results for the control group, there were 6 subjects who underwent 7 angiograms; 1 resulted in CABG, 3 resulted in PCI and the other 3 had coronary disease described as non-obstructive or between 58-69% stenosis. Of note the asterisks in the text above and figure 6 represent the same patient who underwent two angiograms.

For the 4 subjects with ST elevation on ECG at the time of presentation the time-to-door was between 1.2-4.5 days. For the 2 subjects who presented with symptoms, positive biomarkers, and coronary thrombus/plaque rupture requiring PCI, the time to door was 4.5 to 7.7 days.

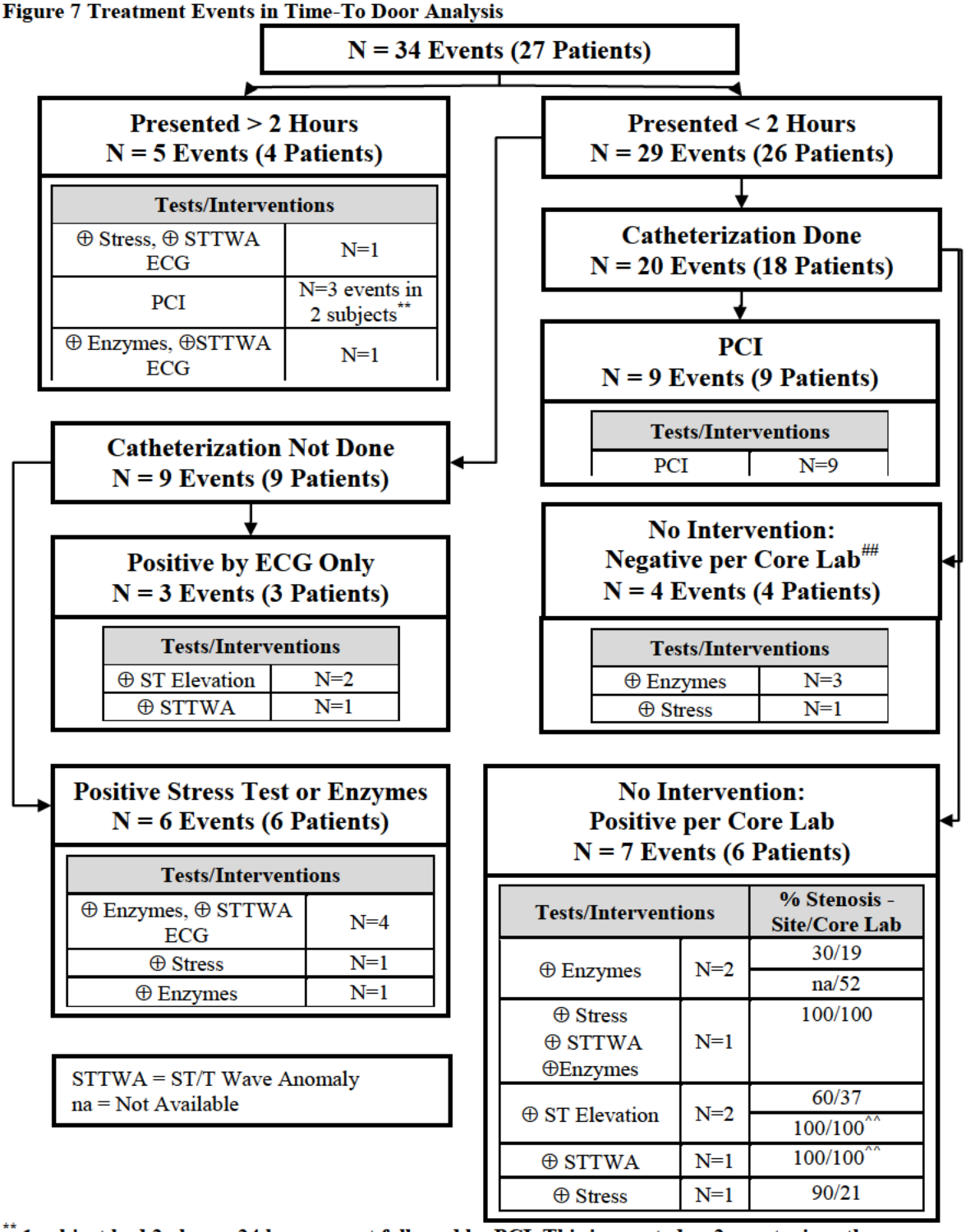
FDA Commentary 5:
Although there were 4 control subjects who presented with ECG changes, these changes were ST depressions and T wave changes rather than ST elevation and therefore do not meet the AGEA definition for a positive standard of care test. One of these 4 control subjects had both a time to door > 2 hours and a new Q Wave event and therefore this subject should not be removed from the analysis. If the remaining 3 are removed from the > 2 hour calculation, then there are 14 control subjects who are included in this analysis, all of whom had a time-to door > 2 hours.

There were 34 alarm events in 27 treatment subjects who had a time-to-door event. Of these 34 events, 29 had a time to door within 2 hours and 5 had a time to door > 2 hours. Of those that presented within 2 hours, 20 underwent an angiogram; 9 received a PCI/stent, 7 were felt to be positive by the Core Lab but no intervention was done, and 4 were deemed a negative angiogram. There were 3 subjects that were positive by ECG only, one of which was due to ST depression. Of the 4 subjects who had 5 time-to-door events > 2 hours, 2 resulted in PCI (one patient had 2 alarms 24 hours apart and a single PCI procedure).

For the 27 treatment arm subjects that had 34 alarms for an ST segment shift and a per protocol clinical ischemic event, they met criteria by the following;

- Of the 27 subjects, 22 had 1 alarm event, 3 subjects had 2 alarm events; 2 subjects had 3 alarm events
- 10 subjects underwent PCI for 12 alarms, one presented > 2 hours, 1 presented both > 2 hours and < 2 hours; 1 also underwent subsequent CABG
- There were 10 angiograms in 10 subjects for 11 alarms where the subject did not undergo PTCA/stent placement; four of which were negative angiograms by Core Lab criteria however one of these subjects had received lytics prior to the angiogram. Five of these subjects did have positive biomarkers; two had a positive stress test and 1 had both positive enzymes and stress test.
- There were 3 alarms that corresponded to ST changes on ECG; 1 of which was ST depression
- There were 8 alarms that corresponded to either a positive stress test or positive biomarkers but an angiogram was not done.

Figure 7 Treatment Events in Time-To Door Analysis



** 1 subject had 2 alarms 24 hours apart followed by PCI. This is counted as 2 events since there were 2 separate alarms

1 Subject received thrombolytic therapy

^^ The same subject had STTWA and then ST Elevation 24 hours later. This counted as 2 events since there were two separate alarms

FDA Commentary 6:
Although there were 3 subjects who presented with ECG changes only, 1 of these was due to ST depressions which does not meet the AGEA definition for a positive standard of care test. Although this subject presented in < 2 hours and therefore is not included in the > 2 hour calculation, it is not clear that this event should be counted as a true positive towards the PPV calculation (see section 8.4).

Table 10 Incidence of Time-to-door >2 hours for a thrombotic coronary occlusion event

		Alerting OFF Group (N=456)		Alerting ON Group (N=451)	
		n	Pts (%)	n	Pts (%)
Look-back Window	7-Day	446	8 (1.8%)	439	4 (0.9%)
	10-Day	446	9 (2.0%)	439	4 (0.9%)
	30-Day	446	13 (2.9%)	439	4 (0.9%)
	50-Day	446	15 (3.4%)	439	4 (0.9%)
	70-Day	446	16 (3.6%)	439	4 (0.9%)
	90-Day	446	17 (3.8%)	439	4 (0.9%)

8.3.1.4 Composite Primary Effectiveness Endpoint

The incidence of composite primary effectiveness endpoint events and the posterior probability of event reduction in the Alerting ON (Treatment) group were computed. Results are shown in
Table 11 using different look-back period windows for late arrival. The sponsor indicated that the change in the number of events among Alerting OFF (Control) subjects from 21 to 29 is due to the arrival of many of these Alerting OFF (Control) subjects more than seven days after Guardian detection. With all Alerting OFF (Control) subject late arrivals counted (90 day look-back), and using the original single baseline primary endpoint data from Table 11, the sponsor concluded the posterior probability of 0.974 didn't meet the threshold for statistical significance which is pre-specified as 0.983.

Table 11 Composite Primary Effectiveness Endpoint Results – Uses Single Baseline New Q Wave Data

Look-back Window	Alerting OFF Group (N=456)		Alerting ON Group (N=451)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	N	Pts (%)	n	Pts (%)	(Completers Only)	(Completers Only)
7-Day	428	21 (4.9%)	423	16 (3.8%)	(-3.93%, 1.67%)	0.7856
10-Day	428	22 (5.1%)	423	16 (3.8%)	(-4.22%, 1.48%)	0.8279
30-Day	428	25 (5.8%)	423	16 (3.8%)	(-5.02%, 0.84%)	0.9177
50-Day	428	27 (6.3%)	423	16 (3.8%)	(-5.55%, 0.43%)	0.9527
70-Day	428	28 (6.5%)	423	16 (3.8%)	(-5.82%, 0.24%)	0.9644
90-Day	428	29 (6.8%)	423	16 (3.8%)	(-6.06%, 0.03%)	0.9740

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

8.3.1.5 Missing Data Imputation

As pre-specified in the SAP, subjects with missing 6-month outcomes have their 6-month outcomes imputed according to a statistical model. Two different prediction methods were used. The pre-specified method "from last known state" imputes the missing event status based on observed event status in the previous follow-up visits. An alternate method was used by the sponsor to group all subjects with missing 6-month outcomes still in the "Start" state at the conclusion of the study. Table 12 and Table 13 show neither missing data imputation analysis can demonstrate the evidence of event rate being lower in the treatment group as none of posterior probability met the threshold of 0.983 for primary effectiveness endpoint.

Table 12 Results of Missing Data Imputation Analyses, Protocol Metric with 7-day Look-back Window

Status at 6 Months	Alerting OFF Group (N=456)	Alerting ON Group (N=451)	Predication Method	95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)^*$
Events: Event-free: Missing:	21 (4.6%) 407 (89.3%) 28 (6.1%)	16 (3.5%) 407 (90.2%) 28 (6.2%)	Pre-specified (from last known state)	(-3.72%, 1.79%)	0.7518
			Alternate (from starting state)	(-3.94%, 1.67%)	0.7858
			None (completers only)	(-3.93%, 1.67%)	0.7856

Table 13 Results of Missing Data Imputation Analyses, Protocol Metric with 90-day Look-back Window

Status at 6 Months	Alerting OFF Group (N=456)	Alerting ON Group (N=451)	Predication Method	95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)^*$
Events: Event-free: Missing:	29 (6.4%) 399 (87.5%) 28 (6.1%)	16 (3.5%) 407 (90.2%) 28 (6.2%)	Pre-specified (from last known state)	(-5.79%, 0.20%)	0.9662
			Alternate (from starting state)	(-6.07%, 0.03%)	0.9737
			None (completers only)	(-6.06%, 0.03%)	0.9740

8.3.2 Post-hoc Analysis using Dual Baseline

8.3.2.1 New Q-Wave MI detected on ECG using the Post Hoc Dual Baseline Analysis

During the course of the study, it became apparent that single isolated Q waves could be present on an ECG and then absent on a subsequent ECG. Therefore, these particular Q waves could not be representative of a true MI which is a permanent condition. It was appreciated that Q waves which come and go may be due to ECG electrode placement or other non-physiologic factors. Therefore, a dual baseline ECG approach was designed which used in addition to the randomization ECG, a pre-implant ECG which was typically done between enrollment and implant. Both the pre-implant and the randomization ECGs had to be in agreement with each other in terms of Q waves that are present. Only Q waves that were absent, then became present, and remained present throughout the study were included in the dual baseline New Q Wave MI endpoint. In

order to accomplish this analysis, the ECG Core Lab performed serial ECG reads for a given subject while remaining blinded to treatment arm. This is illustrated by Table 4 and Table 5 shown above.

Therefore the dual baseline ECG approach used two different baseline ECGs and a serial ECG review process to determine which subjects had developed a new Q wave ECG. This resulted in the new Q wave results changing in 4 subjects. There were 13 (instead of 14) new Q waves in the control group (3.0%) and 7 (instead of 10) new Q waves in the treatment group (1.7%).

Table 14 Incidence of New Q Wave MI

Baseline Used	Alerting OFF Group (N=456)		Alerting ON Group (N=451)	
	n	Pts (%)	n	Pts (%)
Single – At Randomization	427	14 (3.3%)	420	10 (2.4%)
Dual – Pre-Implant and At Randomization	427	13 (3.0%)	420	7 (1.7%)

8.3.2.2 Post-hoc composite endpoint analysis

Table 15 shows the post-hoc primary effectiveness analysis using the dual baseline, ECG analysis. When using these dual baseline, ECG results as part of the composite primary effectiveness endpoint, and a look back window of 7 days the primary effectiveness endpoint was not met. However, when using the dual baseline ECG approach in combination with a look back window of at least 70 days, the primary endpoint, which is pre-specified as a posterior probability of 0.983, is met.

Table 15 Composite Primary Endpoint Results – Uses Dual Baseline New Q Wave Data

Look-back Window	Alerting OFF Group (N=456)		Alerting ON Group (N=451)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	n	Pts (%)	n	Pts (%)	(Completers Only)	(Completers Only)
7-Day	428	20 (4.7%)	423	13 (3.1%)	(-4.28%, 1.02%)	0.8833
10-Day	428	21 (4.9%)	423	13 (3.1%)	(-4.56%, 0.84%)	0.9110
30-Day	428	24 (5.6%)	423	13 (3.1%)	(-5.36%, 0.23%)	0.9637
50-Day	428	26 (6.1%)	423	13 (3.1%)	(-5.89%, -0.18%)	0.9812
70-Day	428	27 (6.3%)	423	13 (3.1%)	(-6.16%, -0.38%)	0.9870
90-Day	428	28 (6.5%)	423	13 (3.1%)	(-6.43%, -0.60%)	0.9908

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

FDA Commentary 7:
The per-protocol analysis shows that primary effectiveness objective was not met and ALERTS study failed to meet the criterion of establishing superiority. Caution should be given when interpreting dual baseline post-hoc analysis since dual baseline was proposed after the sponsor saw the data. The treatment effect could be overestimated due to the use of dual baseline.

8.3.3 Correlation of a Guardian alert to an urgent unplanned cardiac catheterization

There were 33 emergent catheterizations for symptoms and 19 for symptoms plus an alarm. There were 24 urgent catheterizations for an alarm only. Of the 43 catheterizations

that correlate to a preceding alarm with or without symptoms, 20 underwent a coronary intervention, 2 had coronary occlusion with no intervention, and 1 had vasospasm, and 1 had a 78% stenosis with no intervention. The remaining 19 had minimal disease (18) or a 60% stenosis (1) per the Core Lab. Of the 33 catheterizations done for symptoms only, 10 underwent a coronary intervention, and there were two with significant in stent restenosis, and one 100% occlusion of a bypass graft. There were 11 Control group subjects who had 12 catheterizations done for symptoms as well as based upon the clinical assessment at the time of presentation which resulted in 7 PCI/stent interventions and the other 5 catheterizations showed coronary disease ranging from minimal to 69%.

There were 5 STEMIs during the trial. Three were in the treatment group. One had an alarm 15 minutes after arrival and the other 2 were 47 and 103 minutes respectively prior to presentation. For the 2 STEMIs in the control group, 1 had an alert 13 hours after arrival to a medical center and the other was 4 days prior to presentation.
There were 8 ACS events associated with plaque rupture, 7 of which had an alarm or detection.

Of the 179 alarms in 96 subjects in the treatment group during the trial, 34 underwent an angiogram and 22 underwent PCI or lytics (if a subject had several alarms which resulted in 1 angiogram, the angiogram was counted only once for this calculation).

8.3.4 Subgroup Analysis on the primary effectiveness endpoints

8.3.4.1 Race Effect

Table 16 shows the frequentist analysis of race effect between two groups. The sponsor also did the similar analysis using 90-day look-back window and dual baseline, separately. The sponsor concluded that all analysis shows there was no race effect with the primary effectiveness outcomes.

Table 16 Effect of Race on Primary Outcome (protocol metric, 7-day look-back window)

Race	Alerting OFF		Alerting ON		Combined	
	n	Events (%)	n	Events (%)	n	Events (%)
Black	32	3 (9.4%)	27	1 (3.7%)	59	4 (6.8%)
Caucasian	367	15 (4.1%)	366	15 (4.1%)	733	30 (4.1%)
Hispanic	27	2 (7.4%)	22	0 (0.0%)	49	2 (4.1%)
Other	2	1 (50.0%)	8	0 (0.0%)	10	1 (10.0%)
Total	428	21 (4.9%)	423	16 (3.8%)	851	37 (4.3%)
Test of whether outcomes differ by race						
	Fisher-Halton-Freeman Exact Test				P = 0.3584	
Test of whether race effect differs by treatment group						
	Zelen's exact test of common odds ratio				P = 0.1539	

8.3.4.2 Gender Effect

Gender effect between two groups was analyzed using frequentist approach in Table 17. The sponsor concluded the effect of alerting does not differ by gender. However, pooled across both cohorts, females (event rate: 6.7%) exhibited a higher incidence of primary endpoint events than did males (event rate: 3.3%). Adjusting for covariates in a logistic regression model does not change the fact that females have higher incidence than males.

However, the difference was smaller in the Alerting ON group. Similar patterns were observed when 90-day look-back window or dual baseline was used in the subgroup analysis for gender effect.

Table 17 Effect of Gender on Primary Outcome (protocol metric, 7-day look-back window)

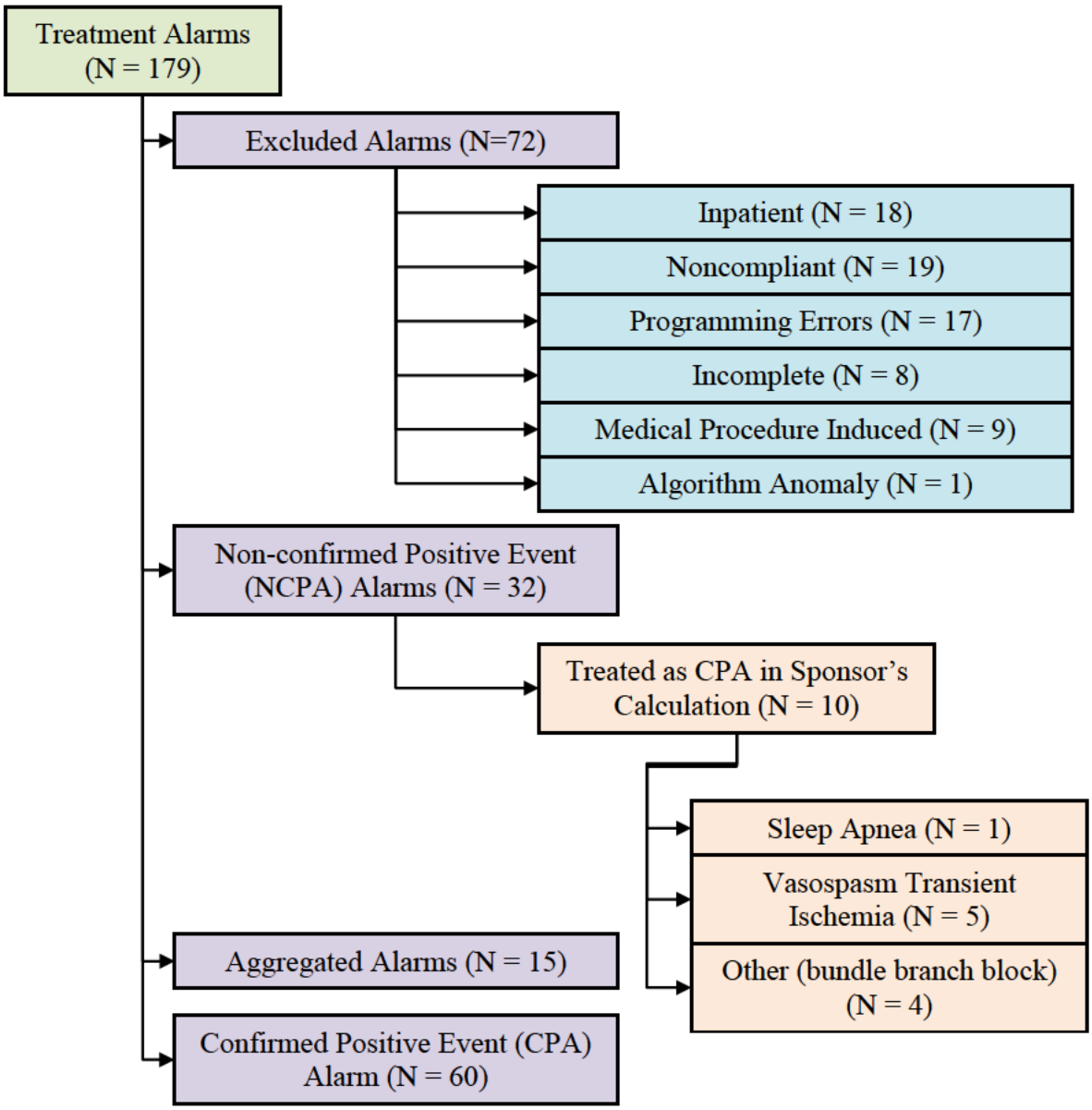
Gender	Alerting OFF		Alerting ON		Combined	
	n	Events (%)	n	Events (%)	n	Evts (%)
Female	144	12 (8.3%)	126	6 (4.8%)	270	18 (6.7%)
Male	284	9 (3.2%)	297	10 (3.4%)	581	19 (3.3%)
Total	428	21 (4.9%)	423	16 (3.8%)	851	37 (4.3%)
Test of whether outcomes differ by gender (pooled treatment groups)						
	Fisher's Exact Test				0.0298	
Test of whether treatment effect differs by Gender						
	Zelen's exact test of common odds ratio				0.4969	

8.4 PPV Calculation

Since it is not possible to quantify the precise true negative or false negative rates in the ALERTS study, it was agreed between FDA and the sponsor to calculate the positive predictive value (PPV). The PPV is the proportion of true positives/true positives+false positives. In this case, the true positives are termed "Confirmed Positive Alarms (CPA)" and the false positives are termed "Non-Confirmed Positive Alarms (NCPA)".

Among 179 alarms in the treatment group, 72 were treated as invalid/inconclusive alarms and therefore were removed from the PPV calculation. In addition, there were 15 alarms that occurred within 72 hours of a previous alarm for the same patient and therefore were aggregated with the prior alarm rather than be counted separately in the PPV calculation. Figure 8 shows the distribution of all 179 alarms in the Treatment group.

Figure 8 Distribution of Treatment Alarms in PPV Calculation



There were 10 alarms which did not correspond to a positive standard of care test; 1 was detected during sleep in a patient non-compliant with CPAP, 4 were new QRS widening on ECG, and 4 were a diagnosis of vasospasm per a cardiologist review of the intracardiac waveforms without ECG or other corroborating testing.
FDA and the Sponsor calculated the PPV differently where FDA did not count these 10 alarms as CPA whereas the sponsor did. Table 18 shows the two different PPV calculation methods. For the FDA recommended method, CPA is defined as one or more of the criteria listed in Section 6.3 and therefore 60 out of 179 treatment alarms were treated as confirmed positive event alarms.

Table 18 PPV Calculations

	PPV Point Estimate*	PPV Point Estimate**	PPV 95% CI**
FDA-Recommended Method	65.2% (60/92)	65.3%	(54.2%, 74.9%)
Sponsor's Method	76.1% (70/92)	77.4%	(67.0%, 85.2%)

*** Estimate Based on raw Counts**

**** Estimate from GEE model to account for within patient correlation**

The following table shows the alert types that were classified as CPAs and NCPAs in both the FDA recommended PPV (which adhered to all FDA guidelines) and the Sponsor PPV calculation.

Table 19 Alert Code Counts

FDA	Sponsor	Count	Alarm Code Definitions
NCPA	CPA	4	Other Relevant Medical condition (i.e., bundle branch block (BBB))
CPA	CPA	60	Confirmed Positive Alarms (Stress/ECG/Enzyme/Site Cath/Core Lab ECG/Core Lab Angio)
NCPA	CPA	5	Vasospasm Transient Ischemia
Excluded	Excluded	8	Excluded Alarm – Standard of Care Testing Not Complete
Excluded	Excluded	1	Excluded Alarm – Algorithm Anomaly Corrected
NCPA	NCPA	1	Algorithm Anomaly Not Corrected
Excluded	Excluded	17	Excluded Alarm – Programming Error Corrected
NCPA	NCPA	14	Negative for Stress/ECG/ Enzyme/Site Cath/Core Lab ECG/Core Lab Angio
Excluded	Excluded	9	Excluded Alarm – Medically Induced by Procedure (Stress test, Cardiac Catheterization, Cardioversion, PCI)
NCPA	NCPA	3	Lead dislodgement, Improper Connection, Device Problem
Excluded	Excluded	19	Excluded Alarm – Subject Non-Compliant
Excluded	Excluded	18	Excluded Alarm – Occurred while subject was Inpatient
NCPA	NCPA	1	Sleep Apnea non-compliance
NCPA	NCPA	4	Symptoms only (no other confirmatory tests)
Aggregate	Aggregate	15	Aggregated – combined with prior Alarm
		179	Total

FDA Commentary 8:

The percentage of excluded alarms is relatively high (72/179=40%), which makes the interpretation of PPV challenging. In addition, the PPV calculation depends heavily on what is classified as a true positive event, which per the protocol uses the AGEA criteria and would likely be lower if a strict guideline-based definition of ACS had been used.

8.5 Secondary Endpoints

There were six pre-specified secondary endpoints. Three of these are the individual components of the composite primary effectiveness endpoint. Multiplicity adjustments were conducted to control the probability of a false positive finding. Tables 20, 21, and 22 show the results for the three individual components of the primary endpoint. The time to door component, when treated as a binary occurrence (>2 hours, < 2 hours) was statistically significant (posterior probability=0.9978). The other two components, new Q wave MI and Cardiac/unexplained death, were not significant.

Table 20 New Q Wave Myocardial Infarction (MI) Component of Primary Objective

Baseline ECG	Alerting OFF Group (N=456)		Alerting ON Group (N=451)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	n	Events (%)	n	Events (%)	(Completers Only)	(Completers Only)
Original Baseline	427	14 (3.3%)	420	10 (2.4%)	(-3.24%, 1.42%)	0.7783
Dual Baseline	427	13 (3.0%)	420	7 (1.7%)	(-3.57%, 0.72%)	0.9015

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

Table 21 Summary of Time-to-Door Events as Binary Occurrences (using various look-back windows)

Look-back Window	Alerting OFF Group (N=456)		Alerting ON Group (N=451)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	n	Events (%)	n	Events (%)	(Completers Only)	(Completers Only)
7-Day	446	8 (1.8%)	439	4 (0.9%)	(-2.57%, 0.73%)	0.8614
10-Day	446	9 (2.0%)	439	4 (0.9%)	(-2.85%, 0.55%)	0.9062
30-Day	446	13 (2.9%)	439	4 (0.9%)	(-3.99%, -0.18%)	0.9840
50-Day	446	15 (3.4%)	439	4 (0.9%)	(-4.53%, -0.54%)	0.9939
70-Day	446	16 (3.6%)	439	4 (0.9%)	(-4.79%, -0.73%)	0.9964
90-Day	446	17 (3.8%)	439	4 (0.9%)	(-5.06%, -0.91%)	0.9978

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

Table 22 Summary of Cardiac or Unexplained Death as Binary Occurrences

Cardiac or Unexplained Death	Alerting OFF Group (N=456)		Alerting ON Group (N=451)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	n	Events (%)	n	Events (%)	(Completers Only)	(Completers Only)
	447	1 (0.2%)	441	3 (0.7%)	(-0.58%, 1.63%)	0.1830

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

The remaining three secondary endpoints are discussed in the sections that follow. They include two endpoints in a subgroup of patients felt to be at high risk for silent MI or silent ischemic events. These are; (1) new Q wave at 6 months, and, (2) the combined endpoint of time to arrival > 2 hours for an alarm due to a confirmed event or a new Q wave at 6 months. Lastly, the sixth secondary endpoint evaluates whether the alert reduces the median time to arrival for a patient with a CPA using the time to door as a continuous variable rather than binary (> 2 hours).

8.5.1 Subjects at High Risk for Silent MI: New Q-wave Myocardial Infarction

The pre-specified High-Risk Subset consists of the 502 subjects who have at least one of the following conditions shown in Table 23:

Table 23 Summary of Subjects in the High Risk Subset

	Alerting OFF Group	Alerting ON Group
Diabetes	224	206
Female ≥ 65 years old (at randomization)	46	46
Previous silent MI	28	25
Total*	261	241

*** Categories are not mutually exclusive**

For the High-Risk Subset, Table 24 summarizes the incidence of a New Q Wave at 6 months. The posterior probability $P_r(R_{ON} < R_{OFF} \mid data)$ is 0.8867 when using the original baseline and 0.9470 when using the dual baseline. These results were not statistically significant.

Table 24 Incidence of New Q Wave MI, High Risk Cohort

Baseline ECG	Alerting OFF Group (N=261)		Alerting ON Group (N=241)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
	N	Evts (%)	N	Evts (%)	(Completers Only)	(Completers Only)
Original Baseline	243	12 (4.9%)	222	6 (2.7%)	(-5.87%, 1.41%)	0.8867
Dual Baseline	243	11 (4.5%)	222	4 (1.8%)	(-6.11%, 0.59%)	0.9470

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

8.5.2 Subjects at High Risk for Silent MI: New Q-wave Myocardial Infarction or Time to Door > 2 hours for Confirmed Thrombotic Coronary Occlusive Event

Table 25 summarizes the incidence of a New Q Wave or Time-to-Door > 2 hour event at 6 months, as the look-back window and choice of baseline ECG analysis method vary for the High-Risk Subset. Using the original baseline and the 7-day look-back window, the posterior probability of a lower incidence in the Alerting ON group is 0.8542 while using the dual baseline with a 90-day look-back window results in a posterior probability of 0.9741. Therefore, this endpoint was not significant regardless of the look back window used or the ECG analysis used.

Table 25 Summary of New Q Wave or Time-to –Door events, High-Risk Cohort

Baseline/Look-back Window		Alerting OFF Group (N=261)		Alerting ON Group (N=241)		95% BCI (ON-OFF)	Posterior Prob. $P_r(R_{ON} < R_{OFF} \mid data)$*
		N	Evts (%)	N	Evts (%)	(Completers Only)	(Completers Only)
Original Baseline	7-Day	243	14 (5.8%)	222	8 (3.6%)	(-6.13%, 1.85%)	0.8542
	10-Day	243	14 (5.8%)	222	8 (3.6%)	(-6.13%, 1.85%)	0.8542
	30-Day	243	15 (6.2%)	222	8 (3.6%)	(-6.60%, 1.51%)	0.8927
	50-Day	243	15 (6.2%)	222	8 (3.6%)	(-6.60%, 1.51%)	0.8927
	70-Day	243	16 (6.6%)	222	8 (3.6%)	(-7.09%, 1.17%)	0.9217
	90-Day	243	17 (7.0%)	222	8 (3.6%)	(-7.55%, 0.78%)	0.9446
Dual Baseline	7-Day	243	13 (5.3%)	222	6 (2.7%)	(-6.38%, 1.06%)	0.9196
	10-Day	243	13 (5.3%)	222	6 (2.7%)	(-6.38%, 1.06%)	0.9196
	30-Day	243	14 (5.8%)	222	6 (2.7%)	(-6.89%, 0.71%)	0.9449
	50-Day	243	14 (5.8%)	222	6 (2.7%)	(-6.89%, 0.71%)	0.9449
	70-Day	243	15 (6.2%)	222	6 (2.7%)	(-7.35%, 0.37%)	0.9616
	90-Day	243	16 (6.6%)	222	6 (2.7%)	(-7.84%, 0.03%)	0.9741

*** R_{ON} and R_{OFF} denote the incidence of events at 6 months in the Alerting ON and OFF populations**

8.5.3 Reduction in Time to Arrival for All Subjects with Confirmed Thrombotic Coronary Occlusive Events

Table 26 displays numerical summaries of the time elapsed from detection to arrival for confirmed thrombotic events as the look-back window varies. In all cases, the posterior probability of superiority is > 0.9999. Therefore, the time to door endpoint, whether analyzed as a binary or continuous variable, is significantly reduced in the Alarm group with a mean time to presentation of 2.66 hours.

Table 26 Summary of Times from Detection to Arrival for Confirmed Thrombotic Event

Look-back Window	Group	Events (Subjects)	Mean ± SD (hours)	Min	Q1	Med	Q3	Max	Pr ($\mu_{ON} < \mu_{OFF}$ | data)
7-Day	OFF	9 (8)	52.33 ± 61.14	1.38	6.61	30.13	67.80	186.03	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	
10-Day	OFF	10 (9)	88.93 ± 86.90	1.38	21.99	56.78	161.52	246.00	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	
30-Day	OFF	14 (13)	322.35 ± 253.68	1.38	78.12	281.97	556.02	717.20	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	
50-Day	OFF	16 (15)	428.51 ± 358.51	1.38	98.76	423.92	623.34	1131.11	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	
70-Day	OFF	17 (16)	570.00 ± 529.99	1.38	109.08	529.91	766.53	1543.63	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	
90-Day	OFF	18 (17)	664.48 ± 640.41	1.38	128.32	532.71	1039.96	1980.44	>0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	0.57	0.85	1.63	26.63	

*** μ_{ON} and μ_{OFF} denote the means of the Alerting ON and Alerting OFF populations**

8.6 Other Endpoints

The ALERTS Clinical Study protocol also included a number of additional pre-specified endpoints as "Other Endpoints" described in Section 6.7. The detailed data for analyses performed for each of those endpoints is presented in Appendix C. Not all of these Other Endpoints were statistically analyzed. When the sample size was considered too small or the results were obviously too close for any difference to exist, the data were not analyzed.

8.7 ALERT Quality of Life (AQOL) Study Results

The ALERTS Quality Of Life (AQOL) study was designed and run as an independent longitudinal prospective study (using separate IRB review and subject consent forms than ALERTS) and recruited a subset of ALERTS Clinical Study subjects from those enrolled during the final 2 years of the ALERTS Clinical Study. The AQOL study enrolled 157 subjects at 26 sites. Patients were paid $100 for each survey completed.

The sponsor used three surveys in their AQOL study: 1) an EuroQOL survey which measures quality of life using the EuroQOL Visual Analog Scale (VAS) and is not cardiac specific. 2) a MacNew QOL survey which is specific to cardiac conditions 3) an AMQOL-FEDU survey that was designed to measure changes in quality of life that are related specifically to Guardian heart-monitoring and alerting. Two versions of the 3 surveys were given; version 1 and as a version 2. Version 1 was given prior to implant

and version 2 was given at 6 and12 months (treatment group) or 12 and18 months (control group) post randomization.

All three surveys showed a significant improvement in quality of life. Specifically, the EuroQOL survey showed a statistically significant improvement at both 6 and 12 months ($p<0.01$). The MacNew also showed positive improvement at 6 and 12 months compared to baseline ($p<0.0001$). And the AMQOL-FEDU demonstrated that patients specifically attributed an improvement in quality of life to the Guardian device including things such as less anxiety and having more control. Almost one-third of patients with the Guardian device reported a decreased use of the emergency department and most attributed this to the Guardian alerting capability. Therefore, there did appear to be an overall improved sense of wellbeing at 6 months which persisted to 12 months for this substudy of subjects.

FDA Commentary 9:
It is unclear how the AQOL study results can be generalized to the entire ALERTS study population since only 15% (157/1020) of the study population participated in the AQOL study. As the AQOL study started in the last two years of ALERTS Clinical study, early patients were not included in the AQOL sub-study.

9 Conclusions

The ALERTS Clinical Study demonstrated that the AngelMed Guardian System met its primary safety endpoint by surpassing the required safety threshold of 0.954 to claim the proportion of subjects free of system-related complications is greater than 90% based on 6 months study data. The proportion of subjects free of system related complications is 97.2% among 910 implanted subjects.

The ALERTS Clinical Study didn't demonstrate the AngelMed Guardian system met the primary effectiveness endpoint. With all Alerting OFF (Control) subject late arrivals counted (90 day look-back), and using the original single baseline primary endpoint data, the sponsor concluded the posterior probability of event reduction was 0.974 (event rate: 3.8% Treatment vs. 6.8% Control) which didn't meet the threshold for statistical significance which is pre-specified as 0.983. Multiple study conduct issues were observed during the course of ALERTS Clinical Study, particularly with respect to the time-to-door and the new Q wave MI endpoints in the composite primary effectiveness endpoint. The quality of the ECG data and the inconsistency of the Q wave results caused the sponsor to terminate the study earlier than the protocol required, and to institute a dual baseline approach with serial reads to the ECG interpretation. The early termination of the ALERTS Clinical Study against protocol is a significant protocol violation which could cause bias and the integrity of the trial may be compromised. The dual baseline post-hoc analysis should be interpreted with caution since use of the dual baseline was proposed after unblinding. The treatment effect could be overestimated due to the use of the dual baseline. The time to door endpoint was also less straightforward than originally anticipated in part because some of the qualifying events such as a positive stress test or disease progression by catheterization in the absence of acute thrombus or plaque rupture are more consistent with ongoing ischemia rather than an ACS event and therefore it is less intuitive what the time course for treatment should be for such events.

FDA looks forward to a productive Panel discussion regarding these issues.

References

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3. Thygesen K, Alpert JS, Jaffe AS, et all on behalf of the ESC/ACCF/AHA/WTF Task Force for the Universal Definition of Myocardial Infarction. Third Universal Definition of Myocardial Infarction JACC 2012:1581-1598.
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APPENDIX A: INCLUSION/EXCLUSION CRITERIA

A.1 INCLUSION CRITERIA

All of the following were required to be enrolled in the ALERTS study:

- Subject has at least one of the following conditions:
- 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.
- Has already undergone coronary angiography and revascularization, unless the physician determines it is appropriate to implant before or during the planned procedure.
- Lives in a geographic area in close proximity (within 60 minutes by EMS) to any hospital that can treat AMI.
- Subjects (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:
    - Post-menopause or amenorrheic during the past year
    - Surgical sterilization
    - Use of effective contraceptive method

A.2 EXCLUSION CRITERIA

Candidates were excluded from the ALERTS study if ANY of the following conditions applied:

- In the investigator's opinion, subject lacks ability to respond appropriately to alarms, e.g., illiteracy, poor memory or cognitive function, dementia or other condition affecting memory function, etc.
- 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.
- 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.
- Subject cannot feel the IMD vibration when placed on top of the skin on the left pectoral side of the chest.
- Subject has recurrent or persistent atrial fibrillation.
- Subject 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.
- Subject has left ventricular hypertrophy evidenced by ECG criteria.
- Subject 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.
- Subject 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.

- There is evidence of unresolved infection (fever > 38o C and/or leukocytosis > 15,000).
- Subject has history of bleeding disorders or severe coagulopathy (platelets < 100,000 plts/ml; APTT or PT > 1.3 x reference range).
- Subject has had a hemorrhagic stroke or transient ischemic attack (TIA) in the past 6 months.
- Subject 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.
- Subject 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 subject's current clinical condition during study procedures.
- Subject 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.
- Subject has experienced gastro-intestinal hemorrhage in the past 6 months.
- Subject has any situation in which the use of aspirin is contraindicated for at least 6 months.
- Subject has epilepsy.
- Subject has known severe allergies, e.g., peanut, bee sting, etc.

APPENDIX B: DEMOGRAPHICS OF ALERTS SUBJECTS

Characteristic	Alerting OFF (Control) Group (N=456)		Alerting ON (Treatment) Group (N=451)		Difference (ON – OFF)
	N	Mean ± S.D. or N (%)	N	Mean ± S.D. or N (%)	95% BCI
Age at Randomization	456	59.5 ± 10.2	451	59.4 ± 10.5	(-1.4, 1.3)
Sex (Female)	456	154 (33.8%)	451	(%)	(-9.4%, 2.7%)
Race/Ethnicity	456		451		
- American Indian		1 (%)		0 (0.0%)	(-1.0%, 0.5%)
- Asian/Pacific Islander		2 (%)		5 (1.1%)	(-0.6%, 2.0%)
- Black – Not of Hispanic Origin		32 (7.0%)		30 (6.7%)	(-3.7%, 2.9%)
- Caucasian – Not of Hispanic Origin		391 (85.7%)		391 (86.7%)	(-3.7%, 5.5%)
- Hispanic – any race		30 (6.6%)		22 (4.9%)	(-4.7%, 1.3%)
- Other		0 (0.0%)		3 (0.7%)	(-0.2%, 1.7%)
Presentation of ACS (Qualifying Event)	456		451		
- STEMI		113 (%)		109 (%)	(-6.2%, 5.0%)
- NSTEMI		127 (%)		126 (%)	(-5.7%, 5.9%)
- Unstable Angina		199 (%)		199 (%)	(-6.0%, 6.9%)
- Other		15 (3.3%)		15 (3.3%)	(-2.4%, 2.4%)
- Unknown		2 (0.4%)		2 (0.4%)	(-1.1%, 1.1%)
History of Silent MI	455	28 (6.2%)	451	25 (5.5%)	(-3.7%, 2.5%)
Diabetes	456	224 (49.1%)	451	206 (45.7%)	(-9.9%, 3.0%)
Dyslipidemia Requiring Medication	456	421 (92.3%)	451	416 (92.2%)	(-3.6%, 3.4%)
Hypertension Requiring Medication	456	426 (93.4%)	451	414 (91.8%)	(-5.1%, 1.8%)
History of Smoking	456	315 (69.1%)	451	322 (71.4%)	(-3.6%, 8.2%)
Currently Smoking	456	121 (26.5%)	451	117 (25.9%)	(-6.3%, 5.1%)
History of Heart Failure	452	60 (13.3%)	451	79 (17.5%)	(-0.5%, 8.9%)
NYHA	452		451		
- I		18 (4.0%)		34 (7.5%)	(0.5%, 6.6%)
- II		32 (7.1%)		36 (8.0%)	(-2.6%, 4.4%)
- III		10 (2.2%)		9 (2.0%)	(-2.2%, 1.8%)
- None		392 (86.7%)		372 (82.5%)	(-9.0%, 0.5%)
Killip Class	448		446		
- I		425 (94.9%)		410 (91.9%)	(-6.3%, 0.4%)
- II		20 (4.5%)		34 (7.6%)	(0.0%, 6.3%)
- III		3 (0.7%)		2 (0.4%)	(-1.4%, 0.9%)
Ejection Fraction (LVEF, %)	418	53.9 ± 8.8	411	54.1 ± 9.4	(-1.1, 1.4)

Characteristic	Alerting OFF (Control) Group (N=456)		Alerting ON (Treatment) Group (N=451)		Difference (ON – OFF)
	N	Mean ± S.D. or N (%)	N	Mean ± S.D. or N (%)	95% BCI
History of Renal Insufficiency	456	75 (16.4%)	451	83 (18.4%)	(-3.0%, 6.9%)
History of Reperfusion/ Revascularization	456	444 (97.4%)	451	442 (98.0%)	(-1.4%, 2.7%)
Angina in previous six months	456	400 (87.7%)	451	395 (87.6%)	(-4.4%, 4.1%)
Average Frequency of Angina	399		394		
- > 10 times/month		63 (15.8%)		58 (14.7%)	(-6.0%, 3.9%)
- 6-10 times/month		44 (11.0%)		37 (9.4%)	(-5.9%, 2.6%)
- 3-6 times/month		87 (21.8%)		101 (25.6%)	(-2.1%, 9.7%)
- < 3 times/month		205 (51.4%)		198 (50.3%)	(-8.0%, 5.8%)
Angina Status (most recent episode as of pre-procedure exam)	398		389		
- Stable		233 (58.5%)		228 (58.6%)	(-6.8%, 6.9%)
- Unstable		165 (41.5%)		161 (41.4%)	(-6.9%, 6.8%)
History of Silent Ischemic Changes	456		451		
- Yes		34 (7.5%)		28 (6.2%)	(-4.6%, 2.1%)
- No		309 (67.8%)		338 (74.9%)	(1.3%, 13.0%)
- Unknown		133 (24.8%)		85 (18.8%)	(-11.2%,-0.5%)
TIMI Risk Score (mean)	454	3.623 ± 0.968	449	3.706 ± 1.023	(-0.048, 0.213)
History of Atrial Arrhythmia	456	25 (5.5%)	450	18 (4.0%)	(-4.3%, 1.3%)
History of Ventricular Arrhythmia	456	26 (5.7%)	450	25 (5.6%)	(-3.2%, 2.9%)
History of Ectopic Arrhythmia	456	6 (1.3%)	450	5 (1.1%)	(-1.8%, 1.4%)

APPENDIX C: SUMMARY OF OTHER CLINICAL ENDPOINTS

Endpoint Objective	Clinical Endpoint	Hypothesis Formula t= Alerting ON (Treatment) c=Alerting OFF (Control)	Results (Units)	Notes
Time From Symptom Recognition to Any Revascularization Treatment for ST Segment Elevation MI (STEMI)	Mean time from system onset to any confirmed revascularization treatment. Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed revascularization time AND documented indication of symptom onset time will be included in this analysis.	H: $\mu_t < \mu_c$	79.5 < 3733 (mean reported in minutes)	Four STEMIs with symptoms (2 Alerting OFF (Control) and 2 Alerting ON (Treatment)) Not Analyzed.
Time From Symptom Recognition to Revascularization Time for all qualifying events.	Mean time from system onset to a confirmed reperfusion treatment. Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed reperfusion time AND documented indication of symptom onset time will be included in this analysis.	H: $\mu_t < \mu_c$	74 < 333 (mean reported in hours)	Twenty-three events (10 Alerting OFF (Control) and 13 Alerting ON (Treatment)). Using Bayesian version of the Wilcoxon rank sum test, the posterior probability of H is 0.9403. So there is borderline evidence that the time from symptoms to revascularization is smaller in the Alerting ON (Treatment) group than in the Alerting OFF (Control) group.
Incidence of Symptom Recognition to Medical Facility Arrival Time > 2 Hours All Visits.	The incidence of patients having an interval between the onset of symptoms and arrival at a medical facility visit that is > 2 hours. Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a documented indication of symptom onset time and facility arrival time will be included in this analysis.	H: $p_t < p_c$	119 < 102 (events)	Not Analyzed.
Incidence of Presentation to the Medical Facility for Ischemic Symptoms with No Confirmed ACS Event.	The incidence of patients presenting to a medical facility due to ischemic symptoms without a confirmed ACS event (positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram). Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented ischemic symptoms will be included in this analysis.	H: $p_t < p_c$	85 < 82 (subjects)	Not Analyzed.
Echocardiographic Ejection Fraction at Discharge Following Recurrent Event	The echocardiographic ejection fraction at discharge AFTER having a confirmed thrombotic occlusive event(positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram) will be recorded for each patient. Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented echocardiographic	H: $\mu_t > \mu_c$	53 > 45 (mean EF %)	25 Alerting OFF (Control) events and 39 Alerting ON (Treatment) group events. Using the prespecified analysis method (Bayesian version of a t-test), the posterior probability of H is 0.9910, with 95% BCI for ($\mu_t - \mu_c$) = (1.51%, 15.28%). So there is statistical evidence that the LVEF is higher at discharge in the Alerting ON

Endpoint Objective	Clinical Endpoint	Hypothesis Formula t= Alerting ON (Treatment) c=Alerting OFF (Control)	Results (Units)	Notes
	ejection fraction value at discharge will be included in this analysis.			(Treatment) group than in the Alerting OFF (Control) group.
Comparisons of the Rates of Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention	The incidence of patients undergoing coronary artery bypass and/or PCI during the first 6 months of the study. Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a documented CABG or PCI procedure will be included in this analysis.	H: $p_t < p_c$	40 > 26 (events)	Posterior Probability Pr($p_t > p_c$) = 0.9736. So there is borderline evidence that the rate is larger in the Alerting ON (Treatment) group than in the Alerting OFF (Control) group.
Guardian System Reduces the Time from Symptom Recognition to Presentation at a Medical Facility for STEMI.	The time from symptom recognition to arrival at a medical facility for a confirmed STEMI event (confirmed as STEMI by ECG CORE Lab)	H: $\mu_t < \mu_c$	23 < 3457 (minutes)	Four STEMIs with symptoms. Not Analyzed.
Guardian System Reduces the Time From the Guardian System Detection to Presentation at a Medical Facility for a STEMI.	Time from Guardian Detection to presentation for ST segment elevation MI (confirmed as STEMI by ECG CORE Lab)	H: $\mu_t < \mu_c$	75 < 6545 (minutes)	Five STEMIs with detections. Not Analyzed.
Guardian System reduces the incidence of any myocardial infarction during follow-up.	The incidence of any myocardial infarction (Q-wave plus Non Q-wave MI) excluding non-Q-wave MI identified within 24-hours of an elective PCI (unless CPKMB>5 x ULN)	H: $p_t < p_c$	3 < 2	Five qualifying events. Not Analyzed.
Guardian System will be Associated With the Detection of a Greater Incidence of Confirmed Plaque Ruptures	The incidence of new plaque ruptures as determined by angiographic core laboratory. The baseline and post-event angiogram(s) of all patients having a detected event that have undergone coronary angiography will be sent to a central blinded angiographic core laboratory for analysis. A patient will be classified as having sustained new plaque rupture if there is a new filling defect or hazy lesion on repeat coronary angiography that was not present at baseline angiography. Plaque rupture will be subcategorized as to whether they required percutaneous coronary intervention (PCI) as well as whether there was pre and post PCI rise in CK or troponin (see MI definition). This includes all patients in both the control and treatment arms of the study.	H: $p > 0.50$	10/12 = 0.83	The posterior probability Pr($p > 0.50$) = 0.9888. 95% BCI for p is (0.5455, 0.9496). So there is statistical evidence that detection of confirmed plaque rupture is higher in the Alerting ON (Treatment) group than in the Alerting OFF (Control) group.
Guardian System will be associated with A Greater Incidence of Significant Disease Progression on Coronary Angiography, IVUS, or Radiographic Studies.	The incidence of significant disease progression as determined by angiographic core laboratory. The baseline and post-event angiogram(s) of all patients having a detected event that have undergone coronary angiography will be sent to a central blinded angiographic core laboratory for analysis. A patient will be classified as having sustained significant disease progression on repeat coronary angiography if there is a change in the percent diameter stenosis of > 20%	H: $p > 0.50$	28/45 = 0.62	With the proportion estimated by 28/45, the posterior probability Pr($p > 0.50$) = 0.9481. 95% BCI for p is (0.4755, 0.7491). So there is borderline evidence that the rate is larger in the Alerting ON (Treatment) group than in the Alerting OFF (Control) group.

Endpoint Objective	Clinical Endpoint	Hypothesis Formula t= Alerting ON (Treatment) c=Alerting OFF (Control)	Results (Units)	Notes
	compared with baseline angiography. Disease progression will be subcategorized as to whether they required percutaneous coronary intervention as well as whether there was pre and post PCI rise in CK or troponin (see MI definition).			
Q waves on Discharge Electrocardiogram Following Recurrent Event	The incidence of patients with a q wave at discharge following a confirmed ACS event (positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram). Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented new q wave will be included in this analysis.	H: $p_t < p_c$	See New Q wave component of primary endpoint data.	No additional work done for this endpoint. See New Q wave component of the primary endpoint.
Abnormal Killip Class at discharge following recurrent event	The incidence of patients being discharged with a diagnosis of abnormal Killip Class AFTER having a confirmed thrombotic occlusive event(positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram). Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented diagnosis at discharge of abnormal Killip Class will be included in this analysis.	H: $p_t < p_c$	8 < 9 (incidents) 6 < 5 (subjects)	Not Analyzed.
Incidence of Clinical CHF at Discharge Following Recurrent Event	The incidence of patients being discharged with clinical CHF diagnosis AFTER having a confirmed thrombotic occlusive event(positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram). Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented diagnosis at discharge of clinical CHF will be included in this analysis.	H: $p_t < p_c$	3 < 1	Not Analyzed.
Combination of clinical CHF/abnormal Killip Class at discharge following recurrent event	The incidence of patients being discharged with either clinical CHF or abnormal Killip Class AFTER having a confirmed thrombotic occlusive event(positive 12 lead ECG, positive cardiac enzyme test, positive stress test, or positive angiogram). Compare treatment to control for the 6 month period starting with randomization and ending with 6 month visit date. Only patients with a confirmed thrombotic occlusive event and documented indication of clinical CHF or abnormal Killip Class at discharge will be included in this analysis.	H: $p_t < p_c$	8 < 5	Not Analyzed.

Endpoint Objective	Clinical Endpoint	Hypothesis Formula t= Alerting ON (Treatment) c=Alerting OFF (Control)	Results (Units)	Notes
*μ_t and μ_c represent means of the Alerting ON (Treatment) and Alerting OFF (Control) populations p_t and p_c represent incidences in the Alerting ON (Treatment) and Alerting OFF (Control) Populations p represents the proportion of confirmed plaque ruptures that are associated with a Guardian System Detection p represents the proportion of instances of significant disease progression that are associated with a Guardian System Detection				