Summary of Safety and Effectiveness Data (SSED)

General Information

Device Generic Name:	Implantable Cardiac Monitor with Patient Alerting
Device Trade Name:	AngelMed Guardian System: **I**mplantable **M**edical **D**evice (IMD) (Version 0.7.4.2) **EX**ternal **D**evice (EXD) (Version 0.7.4) Physician's Programmer (PROG-003) (Version 3.6.3)
Applicant's Name and Address:	Angel Medical Systems, Inc. 1163 Shrewsbury Avenue, Suite E Shrewsbury, NJ 07702
PMA number:	P150009
Date of Panel Recommendation:	**(**To be completed by the FDA)
Date of FDA notice of Approval:	(To be completed by the FDA)

Indication for Use

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

Justification of Indication for Use:

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

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

Contraindications, Warnings, and Precautions

Contraindications

The AngelMed Guardian System is contraindicated for:

- Patients with cognitive issues that would prevent recognition of alarms
- Patients who cannot feel the vibration from the implanted device (IMD)
- Patients with implanted pacemaker, ICD or CRT devices
- Patients where a pacemaker lead cannot be placed safely

Warnings and Precautions

Please refer to the device labeling for warnings and precautions.

Device Description

The Guardian system consists of three main device components shown in Figure 11.4-1:

- Implantable Medical Device (IMD): Permanently implanted in a left pectoral pocket:
  - Collects the patient's electrograms via an endocardial lead
  - Analyzes the electrograms in real time for a variety of cardiac event conditions

  - Vibrates to warn the patient of a cardiac event while signaling the patient's EXD to provide redundant audible and visual external warnings.

  - Stores electrograms for subsequent retrieval by the Programmer via wireless telemetry

- External Device (EXD): A telemetry device given to each patient, which provides redundant auditory and visual alerts via beeps and flashing LEDs. Each Programmer also has a dedicated Wand EXD, which is used for communicating between the Programmer and the IMD.
- Programmer: A specially configured portable computer used to configure the IMD and retrieve and store IMD patient data, including electrograms collected by the IMD.

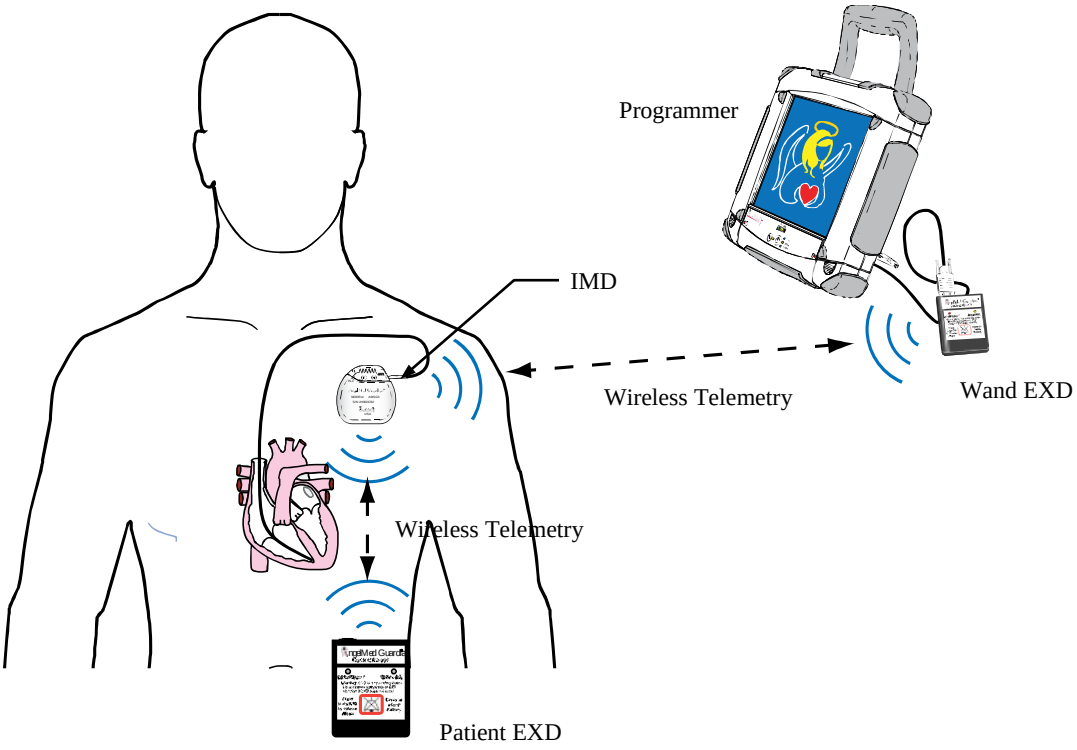

Figure 11.4-1 - The AngelMed Guardian System

IMD

The AngelMed Guardian IMD detects the shift in ST deviation (i.e. the voltage difference between the ST and PQ segment) of the patient's electrogram. The IMD uses Angel Medical

System's detection algorithm to continually monitor the ST deviation of the patients heart beat and compare it with the average ST deviation of the patient.

The IMD supports two basic data acquisition modes: Normal and Post-emergency alarm. The IMD records 10 seconds electrogram segment for every 30 seconds or 90 seconds depending on the characterization of the previous segment.

The size and shape of the IMD is similar to that of the pacemaker. It is approximately 2.0" x 2.2" x 0.42" in height, width, and depth. It also contains a battery and electronic circuit to detect and analyze the patient's ECG and stores the information for the subsequent readout by the physician. The vibration motor in the IMD vibrates to signal an alarm. The functional life of the IMD is minimum 3 years under normal usage conditions. The parts of the IMD are represented in Figure 11.4-2.

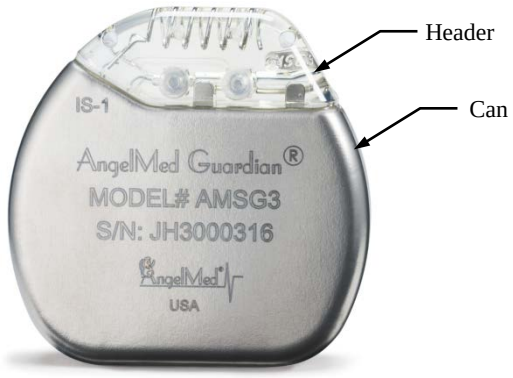

Figure 11.4-2 - AngelMed Guardian IMD

EXD

The size of the EXD is similar to the pager and includes the following parts

- An alarm silence button (which can turn off both the vibratory alarm of the IMD and audible alarm on the EXD)
- Two LEDs to indicate "Emergency" alarm and "See Doctor" alarm
- An internal antenna
- A replaceable battery

- Speaker
- Electronic circuits to communicate with the IMD and the PROG

The average battery life of the EXD is 6 months. Your battery can only be replaced using a battery with a lithium-based chemistry. The parts of the EXD (Front and Back) is represented in Figures 11.4-3 and 11.4-4.

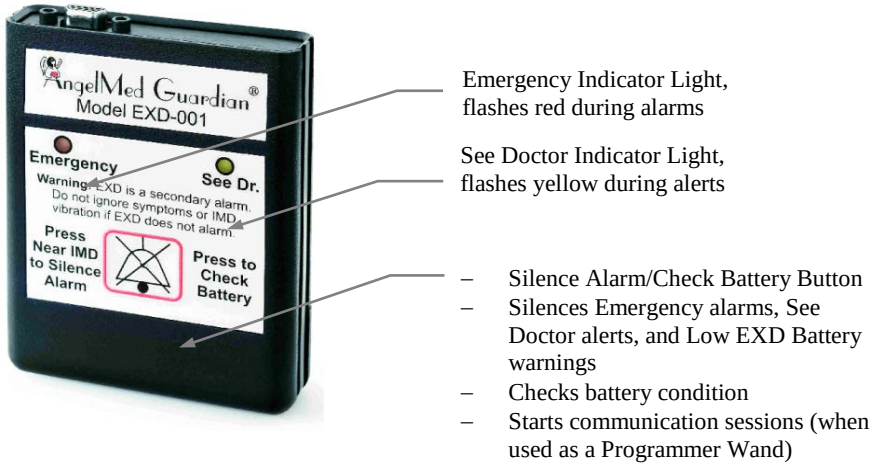

Figure 11.4-3 - AngelMed Guardian EXD (Front)

Back – The back of the EXD contains a metal ring for attaching the neck cord if desired, two instruction fields, and the battery compartment cover.

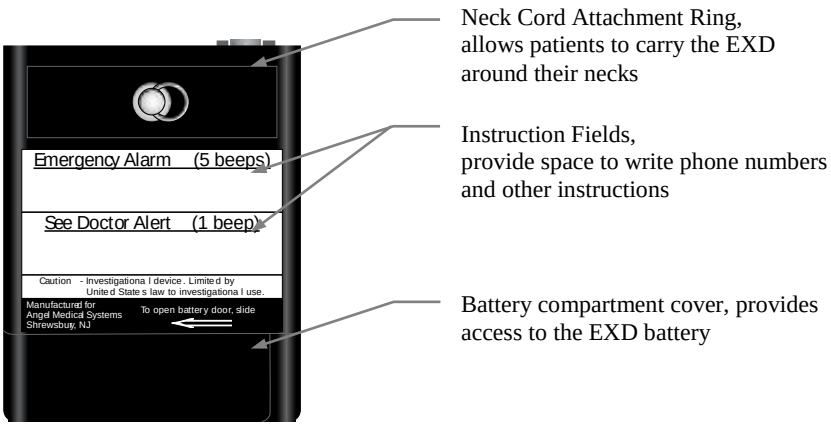

Figure 11.4-4 - AngelMed Guardian EXD (Back)

Programmer (Prog-003)

The Model Prog-003 Programmer (Figure 11.4-5) is a compact and portable device used to program and retrieve patient data from an IMD.

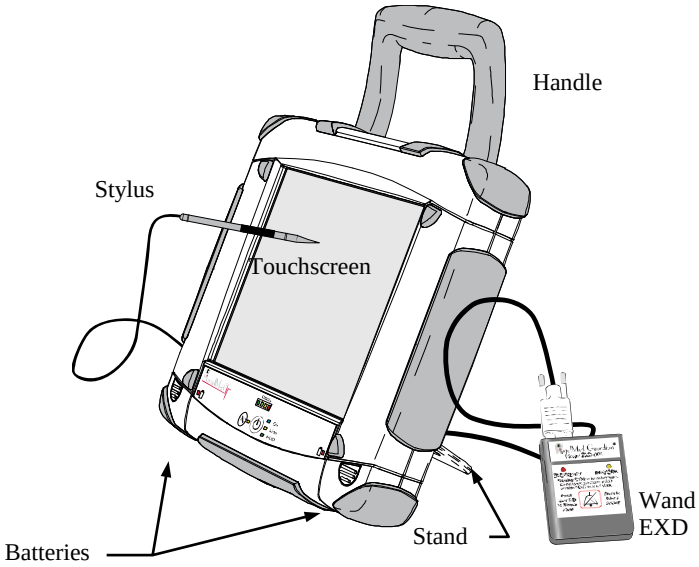

Figure 11.4-5 - AngelMed Guardian Programmer (PROG-003)

Alternative Practices and Procedures

The Guardian System is a novel device designed to alert patients to a detected significant shift in the ST segment deviation (the ST segment to PQ segment voltage difference of the subject's electrogram from the tip of an implanted pacemaker lead) relative to the patient's self-normalized baseline ST segment deviation data, captured the preceding day and indicative of coronary artery occlusion. Only pacemakers, ICDs and CRT devices currently monitor the electrogram from an implanted lead but none are approved to monitor the ST segment or alert patients to detected potential coronary occlusions. The current standard of care for surface electrocardiogram monitoring are the 12 lead ECG and the Holter Monitor but each are used for short durations only and both are susceptible to noise.

Marketing History

The AngelMed Guardian has not been marketed in the United States.

The AngelMed Guardian system is commercially available in Brazil and approved for commercial distribution in the EU (None currently sold). The first commercial implant in Brazil was performed on February 19, 2009. Since that initial implant there have been an additional 49 commercial implants in Brazil. The AngelMed Guardian System had performed very well there with only a handful of minor complaints. In addition there have been no reportable events or unresolved complications related to the device or procedure in commercial use. The AngelMed guardian system obtained CE mark approval in September 2010. The device has not been withdrawn from the market of these countries for any reason.

Potential Adverse Effects of the Device on Health

The AngelMed Guardian IMD is implanted with an FDA approved active fixation IS-1 compatible pacemaker leads such as those listed in Table 11.7-1:

Table 11.7-1 IS-1 Compatible Pacemaker Leads for the AngelMed Guardian System

Manufacturer	Model
St. Jude Medical	Pacesetter Tendril SDX Model 1488T
St. Jude Medical	Pacesetter Tendril SDX Model 1488TC
St. Jude Medical	Pacesetter Tendril SDX Model 1688T
St. Jude Medical	Pacesetter Tendril SDX Model 1688TC
St. Jude Medical	Pacesetter Tendril ST Optim Model 1888
St Jude Medical	Tendril STS lead Model 2088TC
Medtronic	4076 CapSureFix Novus
34, 40, 46, 52, 58, 65, 85, 100 cm lengths	

The implant procedure is identical to that of a single chamber pacemaker where the lead tip is positioned at or near the apex of the patient's right ventricle.

Between 2008 and 2013, the AngelMed Guardian System IMD was implanted in 910 subjects in the ALERTS Clinical Study. Although only 907 were randomized, it is the number successfully

implanted that is relevant to the safety endpoint that was assessed during the period from implant until the subject's 6 month follow-up visit. The ALERTS Clinical Study primary safety endpoint was to demonstrate a better than 90% freedom from system related complications over this period.

Adverse Events/ System Related Complication

The primary safety objective was to establish that the proportion of subjects free of system-related complications is > 90%, at 6 months (i.e. the incidence of system-related complications is < 10%). There were 26 system related complication events in 25 subjects (2.7%) requiring intervention as defined for the primary safety endpoint. All safety events were adjudicated by an independent committee of physicians (the Adverse Events Committee or AEC). A breakdown of the causes for the 26 events are shown in Table 11.7-2. Infections were the largest group with 11 subjects (1.2%).

Table 11.7-2 System Related Complications in ALERTS subjects

	Pooled treatment groups (N = 910)			
	Events	**Subjects**	**%***	**95% BCI**
Infection	11	11	1.2	(0.7, 2.2)
Other System-related complication**	5	5	0.5	(0.2, 1.3)
Pain at or near the pocket site	3	3	0.3	(0.1, 1.0)
Lead migration/dislodgment	2	2	0.2	(0.1, 0.8)
Cardiac perforation	2	2	0.2	(0.1, 0.8)
Erosion	1	1	0.1	(0.0, 0.6)
Loss of sensing due to dislodgement or malfunction of lead	1	1	0.1	(0.0, 0.6)
Visible bump where implanted in the chest	1	1	0.1	(0.0, 0.6)
Total	26	25	2.7	(1.9, 4.0)

* Percentage is # subjects experiencing event / # subjects with successful implant (× 100).

** These 5 events include, lead adapter replacement, 2 early battery failures, subject request for removal due to discomfort, and skin erosion from the lead.

The primary safety endpoint of greater than 90% freedom from system related complications was clearly met. In addition to meeting this objective, it is important to note that there was no lasting

morbidity from any system-related complication in ALERTS, since all safety related issues were resolved over the course of the study.

Table 11.7-3 provides the statistical analysis showing a posterior probability of > **0.9999**, clearly demonstrating statistical significance for the primary safety endpoint.

Table 11.7-3 Analysis of Primary Safety Endpoint	
All Successfully Implanted Subjects (N=910)	
Status at 6 Months: • 25 subjects with 26 events • 870 event-free • 15 unobserved (no event but insufficient follow-up) • % Event-free = 870/(870+25) = 97.2%	
Posterior Probability Pr(R > 0.90 | data) at 6 months (with SAP-specified imputations for missing values)	> 0.9999

Potential Adverse Events

Possible complications of the AngelMed Guardian System include those related to the implantation procedure, and those related to long-term patient tolerance of the implant. There were no unanticipated adverse events reported during the study. Adverse events which may potentially occur are identical to those for a single chamber pacemaker. A complete list of all potential adverse events can be found in the device labeling for the AngelMed Guardian System.

Summary of Preclinical Studies

Laboratory Studies

Risk Analysis

The AngelMed Guardian System was developed in accordance with design controls and a risk management process that conformed with ISO 14971:2000 to identify and manage AngelMed Guardian System hazards and risks and to eliminate risk or reduce it to as low as reasonably practicable given the intended use.

Product Testing

Biocompatibility

The Angel Guardian System has been tested for biocompatibility as recommended by ISO 10993-1:2009 for a device that is categorized as an implant device contacting tissue for more than 30 days. The tests were conducted in compliance with US Food and Drug Administration – Good Laboratory Practice for Non- Clinical Laboratory Studies 21 CFR Part 58. The results of the biocompatibility studies are summarized in the Table 11.8-1 below.

Table 11.8-1 IMD Biocompatibility Testing

Test	Standard	Test Results
Cytotoxicity: MEM elution	ISO 10993-1:2009 ISO 10993-5:2009 ISO 10993-12:2007	The test met the required standards.
Genotoxicity: Ames Test (Solids)	ISO 10993-3:2003 ISO 10993-12:2007	The test met the required standards.
Sensitization: Magnusson-Kligman Method	ISO 10993-10:2010 ISO 10993-12:2007	The test met the required standards.
Irritation: Intracutaneous Toxicity (ISO)	ISO 10993-10:2010 ISO 10993-12:2007	The test met the required standards.
Systemic Toxicity: Systemic Injection (ISO)	ISO 10993-11:2006 ISO 10993-12:2007	The test met the required standards.
Systemic Toxicity: Material Mediated Pyrogen	ISO 10993-11:2006 ISO 10993-12:2007	The test met the required standards.
Genotoxicity: In Vivo Mouse Micronucleus	ISO 10993-3:2003 ISO 10993-12:2007	The test met the required standards.
Genotoxicity: Mouse Lymphoma, per extract	ISO 10993-3:2003 ISO 10993-12:2007	The test met the required standards.
Implant Study	ISO 10993-6:2007/(R) 2010	The test met the required standards.

Packaging, Sterilization and Shelf Life information

The sterile tray contents are sterilized with ethylene oxide and sealed with a Tyvek membrane. Real-time and accelerated aging tests support a 1-year shelf life. A mixture of functional and non-functional units were visually inspected and the functional units tested by AngelMed prior to the packaging testing.

The packaging test, accelerated aging test and the real time aging tests were performed according to the AAMI/ANSI/ISO 11607 standard. Specifically, accelerated and real-time aged units were submitted for the following testing:

- American Society for Testing and Materials (ASTM) Shipping
- ASTM F 1608 Microbial Challenge
- Tensile
- Burst
- Dye
- Visual Inspection (Physical Integrity)

The sterilization validation of the Angel Guardian System, confirmed the sterility assurance level (SAL) by ethylene oxide sterilization according to the EtO Sterilization processes and equipment included in ISO 11135-1:2007.

Mechanical and Electrical Verification

- Battery: The battery was subjected to a series of performance testing including battery capacity verification (longevity) using multiple discharge rates, forced and rapid discharge testing, and environmental testing per UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria (UNDOT), 4th revised edition, section 38.3 (Lithium batteries).
- Feedthrough: The feedthrough utilized in the AngelMed Guardian IMD underwent safety, environmental, physical and electrical verification testing, including hermeticity (helium leak test to verify a leak rate of no greater than 1x10-8 cc-atm/s of helium).

- The IS-1 connector cavity in the header of the AMSG3 IMD meets applicable performance requirements (maximum insertion force, set screw verification, electrical impedance between conducting parts) of the ISO 5841-3:2007 standard.
- Integrated Circuits: Components underwent electrical test after accelerated life test exposure (+80°C for 72 hours).
- Electrical Safety Testing (including amplifier input protection, DC leakage current, protection of damage to the device caused by external defibrillators or diagnostic levels of ultrasound or electrostatic discharge, protection of harm to the patient caused by heat (temperature rise during single fault condition), radiated immunity, energy delivered, energy extracted, etc.) per EN 45502-1:1998.
- Mechanical & Environmental Testing (drop testing, header torque/push-off testing, dimensional, radiopaque identification, operating/storage temperature/humidity, temperature shock, operating/storage atmospheric pressure, operational/transportation vibration, and hermeticity (helium leak test to verify a leak rate of no greater than 1x10-8 cc-atm/s of helium)) per EN45502-1:1998.

Additional testing of the AngelMed Guardian System included:

- Human Factors Testing
    - Vibratory and Auditory Alarm Characteristics
    - Learning and Memory of Emergency Alarms and See Doctor Alerts
    - Usability of the AngelMed Patient Manual
- Programmer User Interface
- Battery Life and End of Service (EOS)

Software Validation

The AngelMed Guardian IMD, EXD and Physician's Programmer software was developed verified and validated according to IEC 62304:2006 and as per the product software requirement specification. Preclinical validation of software as part of the AngelMed Guardian System was performed using simulated user scenarios.

EMC/EMI, Radio and Co-existence Verification

The AngelMed Guardian System EMC/EMI and wireless radio testing was performed per applicable regulations and standards including:

- Electromagnetic Environmental Effects per ASTM F 1608

Wireless co-existence testing of the AngelMed Guardian System was performed in potentially interfering use environments, such as near metal detectors, electronic article surveillance (EAS) systems, radio frequency identification (RFID) readers, and mobile phones.

The conclusion of pre-clinical validation of EMC/EMI, radio and coexistence verification was that the AngelMed Guardian System met its intended use with the necessary contraindications, warnings, precautions, and additional information included in the labeling for the clinician and patient.

Animal Studies

In 2004, initial animal testing in pigs was followed by discussion with, and input from, the FDA on the design of a final pre-clinical GLP animal study. In 2005, the formal GLP study commenced. Eleven pigs were implanted with an RV apical pacemaker lead and the AngelMed Guardian IMD implant. Five pigs were implanted for long-term safety evaluation. Each of the remaining six pigs then received two copper stents in one of the three major coronary arteries. Copper is extremely inflammatory and within 24-48 hours of implant produces a blood clot in the coronary artery mimicking a human acute myocardial infarction. The study demonstrated the ability to sense, detect, and record dramatic, detected ST segment shifts during coronary thrombotic occlusion. The anatomical post-mortem pathology evaluation demonstrated that the Guardian had successfully detected significant ST shifts for all of animals who demonstrated occlusions in LAD, LCX and RCA coronary arteries resulting from a coronary blood clot. The results were published in the Journal of American College of Cardiology in 2006.

Clinical Studies

CARDIOSAVER

There have been six human clinical studies related to the AngelMed Guardian System was developed to provide patient alerting for ischemia and heart rate related cardiac events. These are:

1 A first Proof of Concept Study [1]

2 Human Factors Studies to optimize alerting parameters [2]

3 A First-in-Man Study in Brazil (CARDIOSAVER) [3–6]

4 A US IDE Safety Study (DETECT) [3,4]

5 A Prospective Randomized Pivotal IDE Study (ALERTS) [7]

6 A Quality of Life sub-study in ALERTS subjects (AQOL)

The results of these studies follow.

First Proof of Concept and Human Factors Studies (2001-2004) [1,2]

The first study in humans used a temporary pacemaker lead to measure RV apical voltage (referenced to left pectoral region) during a two-minute occlusion obtained during scheduled balloon angioplasty of 17 lesions in 14 subjects (who were receiving the angioplasty for clinical reasons). This study demonstrated that the ST changes during coronary occlusion as seen from an intracardiac RV apical electrogram were larger than those seen on the skin surface.

It was recognized early in the development of the AngelMed Guardian System, that the primary function of the system would be to alert heart attack patients to take immediate action and quickly call 911 for transportation to a medical facility. Based on the premise that correct compliance to alerting was critical for the Guardian to providing patient benefit, the alerting signals/protocols must be simple and robust, and instructions to patients must be clear. With this in mind, Angel Medical developed the alerting functionality in the Guardian System including vibration from the implanted device (IMD), and sound and flashing LEDs in a pager like external device (EXD). Studies using appropriate elderly subjects were conducted to identify and validate the triple-sensory modality alerting provided by the Guardian system. The patterns and intensities of both the external and internal alerting were evaluated with respect to human factors issues and results used to determine the final alerting that would be appropriate for, and most effective in, the target patient population.

CARDIOSAVER [3–6]

In 2005, 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 had 1) demonstrated ischemia on an exercise stress test and 2) had an angiogram showing a stenosed coronary artery and 3) had a clinical indication for angioplasty and/or stenting. The Guardian was implanted in these subjects and initial programming of the devices was done

shortly after implant. 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 3 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.
The data collected during balloon occlusion clearly showed total coronary occlusion would cause significant intracardiac ST shifts if the vessel stenosis being opened by PCI did not have significant collaterals. These data also showed that occlusion of a stenosis with good collateral flow would not cause significant ST shifts as the downstream tissue was still being fed oxygen by the collateral vessels.

After the implantation and balloon occlusion studies were completed, CARDIOSAVER subjects were sent home with daily ambulatory monitoring and alerting activated, and additional spontaneous coronary occlusive events were then detected. The results of this study were published in the Journal of the American College of Cardiology including data providing the first human examples of Guardian alerting for real-life ischemic events that were caused by vulnerable plaque rupture in a coronary artery. These data were convincing and showed the potential of the implanted AngelMed Guardian to detect acute coronary occlusion in subjects to enable potentially life or heart muscle-saving early coronary intervention/revascularization.

DETECT [3,4]

In late 2006, AngelMed submitted an IDE to the FDA requesting approval to begin a US-based 20 subject safety study with two primary objectives:

- Show that the AngelMed Guardian maintains a high safety profile when implanted in US patients; and

- Demonstrate that the *Autopick* function in the AngelMed Guardian 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 proved the value of the *Autopick* function of the Guardian Physician Programmer. Using the subject's own data as a guide (subject acts as his or her real-time control)

provides for greater ischemia detection specificity since what is normal for one patient may be quite abnormal for another. This approach also helps to normalize thresholds for each individual, which may be particularly important in patients with some degree of incomplete revascularization of their coronary artery disease.

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 showing effectiveness of the Guardian in detecting ST changes from coronary blockages including thrombotic occlusions from ruptured plaques.

Of particular importance in the JACC publication was the evidence from 3 of the 4 Emergency Alarm cases presented of a first transient occlusive event followed at a later time by a more significant event, all related to an IVUS confirmed ruptured plaque.

ALERTS [7]

ALERTS Clinical Study Design

The ALERTS randomized prospective clinical trial was approved under IDE (G060259) by the FDA to test the safety and efficacy of the AngelMed Guardian system by comparing the outcomes for subjects with and without the benefit of alerting following the detection of anomalous changes in the electrogram monitored by an Implantable Medical Device (IMD) through a standard pacemaker lead. For the 6 month randomized period, treatment group subjects would receive alerts from IMD detections, control group subjects would not. Control subjects, however, would have detection enabled and detection related data captured and saved for later review.

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 6 months of subject enrollment.
- Additional risk factors/co-morbidities (diabetes, TIMI risk score > 3, or renal insufficiency).

The reason for this profile was twofold. First, this subject profile had a high risk for a recurrent ACS event so they would derive the most potential benefit from alerting, and second, to provide a sufficient number of events within the ALERTS trial in order to show a significant benefit from alerting.

After enrollment but prior to the Guardian implant, a first baseline (12-lead) ECG was recorded (known as “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 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.

Subjects were randomized 1:1 to the treatment and control groups when they returned to the site for programming of the Guardian IMD 7-14 days after implantation. Both the treatment group and control group subjects had ST shift detection enabled where treatment group subjects had alerting turned “on” and 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 (termed “randomization ECG”).

Following randomization, subjects who were randomized to the treatment group had their Guardian programmed for both detection and alerting and were provided with an EXD. Both

Emergency Alarms and See Doctor Alerts were triggered using the Physician's Programmer for a short duration to train the subject to recognize the alerts and how to silence an alert using the EXD. Treatment subjects were then instructed on how to respond to Emergency Alarms and See Doctor Alerts.

Subjects randomized to the Control group received the standard of care, per the treating physician and site. Both groups received the same education regarding the importance of seeking immediate medical attention should subjective symptoms of an ischemic event occur regardless of whether an alert was issued by the Guardian system. Except for the difference in activating the alerting capability, the Control and treatment subjects had their IMDs programmed in the same way with respect to event detection and collection of related cardiac data. It is important to note that the enablement of ST shift detection and capture of data in the control group allowed the collection of the time and electrogram data associated with what would have been an Emergency Alarm were alerts enabled. This information was essential in determining endpoints in our control patients.

The protocol required all subjects to have follow-up visits at 1, 3, and 6 months, then every 6 months from that point onward. At each visit the subject's IMD event status was uploaded to the Physician Programmer for review, and records of medications taken were updated. Further, subjects reviewed the ALERTS study subject protocol in order to reinforce training on how to correctly respond to Guardian alerting and/or subjective symptoms that may be associated with a heart attack.

For the Control subjects, Guardian alerts were enabled at the 6-month follow-up visit, consistent with the parameters of the treatment subjects programming at 7-14 days (i.e., at 6-months the Control subjects crossed over to "alerting on"). At this time, former control subjects were trained regarding Guardian alerting protocols. At each subject visit, a 12-lead ECG was also obtained, data was retrieved from the IMD, and *AutoPick* was typically evaluated to check/adjust threshold settings as necessary. Any adverse experiences or complications were recorded as well. For the first 6 months of follow-up, the subjects and site staff in the Control group were blinded to the ECG data that was transmitted to the programmer in order to avoid any influence on the treatment of the Control group subjects.

In the event of an Emergency Alarm, upon presentation at a study site, subjects would have the time of symptom onset recorded as well as arrival time at the treatment facility. When no symptoms were present, the symptom onset time was recorded as "null". Regardless of whether chest pain was present or not, subjects having an Emergency Alarm underwent a cardiac evaluation consistent with the standard of care for chest pain. This included serial cardiac enzymes, serial ECGs, recording of adverse events, summary of medications taken or delivered in response to the subject visit. If deemed necessary (or if the initial standard of care tests were inconclusive or ambiguous), the protocol requested the provision of more specific standard of care tests, including stress tests and/or angiography. This was done because the nature of this study benefited from the most definitive results possible with respect to the occurrence of coronary artery occlusions and/or narrowing. Echocardiogram measurements of Left Ventricular Ejection Fraction (LVEF) were collected pre-implant and at the time of discharge for any confirmed thrombotic event.

Two methods are important to understanding of the analysis and results of the ALERTS Clinical Study. These relate to the components of the primary efficacy endpoint of the study.
Two methods are important to understanding of the analysis and results of the ALERTS Clinical Study. These relate to the components of the primary efficacy endpoint of the study.
There are three components of the primary efficacy objective for the ALERTS Clinical Study. These are:

- Cardiac or unexplained death,
- New Q-Wave MI being a new Q-Wave in the 6 month ECG that was not present before randomization of the subject, 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.

The initial ALERTS Clinical Study statistical analysis plan (SAP) approved by FDA in 2008 did not distinguish between the maximum allowable time between ST shift detection and the "late arrival" for a confirmed occlusive event for Control subjects versus treatment subjects. For treatment group subjects, a 2 hour interval was simple to assess, because the Guardian alert starts

a timer and the ER arrival time ends the interval. However, Control group subjects get no such alert to start the timer. For control group subjects, one must begin with an actual ER arrival time that is the end of the interval – and then look back from that arrival time to determine where the interval would have started if alerting had been enabled – by looking for a Guardian detection.

Following an initial IDE supplement that limited the maximum time ("lookback" period) to 7 days, additional publications in 2013 indicated that 7 days was too short and that the presentation of subjects with no symptoms or unrecognized symptoms could be delayed until their next scheduled follow-up that could be as long as 90 days later (i.e. between the 3 and 6 month follow-up visits) in the ALERTS follow-up schedule.

Before unblinding, FDA agreed to allow the sponsor to submit endpoint data with multiple lookback periods. The data presented for primary and many secondary endpoints therefore are presented with maximum lookback periods of 7,10, 30, 50, 70 and 90 days.

ALERTS Statistical and Clinical Analyses Considerations and Methodology

For the population studied in ALERTS, the predicted annual event rate for either reinfarction or sudden death after the index (enrolling) event was 4.8% for patients presenting with STEMI and 5.6% for patients presenting with non–ST-elevation MI/unstable angina. However, as with any new study, there was still uncertainty regarding the rate of events to be expected in the control population as well as uncertainty regarding the size of the treatment effect effect - i.e., the reduction in rate of events that might be observed in the treatment (alerting ON) group as compared to control (alerting OFF) group. To account for this uncertainty, a Bayesian adaptive design was selected so that sample size could be dynamically determined during the course of the trial. The appropriateness of the sample size was to be evaluated at different time points during the trial, with Bayesian prediction of data values for subjects who had not yet reached their 6 month follow-up visit. In order to determine whether to stop or to continue subject accrual, several planned analyses were specified. The first planned analysis was to occur after 600 subjects were enrolled and randomized, with subsequent analyses occurring at every 300 randomizations thereafter to a maximum of 3,000 subjects.

In 2005, while using an adaptive Bayesian statistical approach was very novel, the sponsor and our medical advisors thought it was appropriate. Over time, however, experience and practical reality demonstrated that for a device trial of this magnitude and complexity, the desired benefit of the specified Bayesian predictive model was not realistic, and the approach did not actually accomplish what was intended. Specifically, regarding the New Q wave component of the primary composite endpoint, the premise that an eECG core-lab-identified new Q-Wave in a 1 or 3 month visit would predict with certainty the presence of the new Q-Wave at 6 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 predictive aspect that was specified in the design was neither accurate nor supportable, and the sponsor had to adjust accordingly.

As a result of this, The ALERTS study was stopped after reaching the FDA IDE approved enrollment target of 1020 enrolled subjects. At this point the database was frozen, and the ALERTS study data were statistically analyzed according to the FDA approved Statistical Analysis Plan (SAP).

For the purposes of clarification, Bayesian statistical methods use posterior probabilities instead of p-values to assess the level of evidence in support of a hypothesis. The study statistician provided support for use of a posterior probability of 0.975 or greater as the appropriate threshold for declaring statistical significance for the primary, secondary and other safety and efficacy endpoints of the ALERTS Clinical Study.

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

- **The Adverse Events Committee (AEC)** – an independent committee of physicians who adjudicated all adverse events entered by the ALERTS Clinical Study
- **Medpace** - Medpace served as the ALERTS study clinical research organization (CRO) who was responsible for obtaining data from sites and interfacing between, and allowing

minimal interaction between, the sponsor, the Core Laboratories, and the committees, and the study statistician.

- **The ALERTS Group for Endpoint Adjudication (AGEA) -** an independent committee of physicians who identified positive clinical events for inclusion as eligible confirmed thrombotic occlusive events for the Time to Door > 2 hours component of the composite primary endpoint.
- **The eECG Core Laboratory at the Duke Clinical Research Institute -** a 12-lead ECG core lab that performed all 12-lead ECG analyses for the ALERTS Clinical Study:
- **The Angiography Core Laboratory at The PERFUSE Study Group**, Harvard Medical School – an angiographic core lab that performed all analyses of angiograms obtained during cardiac catheterization procedures performed during the ALERTS Clinical Study.
- **Data Safety Management Board (DSMB) –** an independent committee of experts from various disciplines who were responsible for monitoring the overall conduct of the study.

In accordance with the SAP and after adjudication of all events (by the ALERTS Group for Endpoint Adjudication (AGEA) Committee), angiograms by the PERFUSE core lab, and all ECGs by the eECG Core Laboratory at the Duke Clinical Research Institute (using serial review of pre-implant, at randomization, 1, 3 and 6 month ECGs), the results were reported as posterior probabilities by the ALERTS study statistician.

ALERTS Clinical Study Results

ALERTS Primary Safety Endpoint

The primary safety objective was to establish that the that the proportion of subjects free of system-related complications is > 90%, at 6 months (i.e. the incidence of system-related complications is < 10%)

The primary safety endpoint of greater than 90% freedom from system related complications was clearly met. In addition to meeting this objective, it is important to note that there was no lasting morbidity from any system-related complication in ALERTS, since all safety related issues were resolved over the course of the study.

Table 11.9-1 provides the statistical analysis showing a posterior probability of **> 0.9999**, clearly demonstrating statistical significance for the primary safety endpoint.

Table 11.9-1 Analysis of Primary Safety Endpoint	
All Successfully Implanted Subjects (N=910)	
Status at 6 Months: • 25 subjects with events • 870 event-free • 15 unobserved (no event but insufficient follow-up) • % Event-free = 870/(870+25) = 97.2%	
Posterior Probability Pr(R > 0.90 | data) at 6 months (with SAP-specified imputations for missing values)	>0.9999

ALERTS Clinical Benefits: Reducing Time- to-door

It is unanimous among the medical community that reducing time from coronary occlusion to treatment for heart attacks will be clinically beneficial to a patient's overall outcome.

The ALERTS Clinical Study is the first study ever conducted that could capture the time delay from detection of coronary occlusion to arrival at a medical facility. For the ALERTS Clinical Study control subjects, as with all heart attack patients today, the only prompt that will cause a patient to seek medical attention for a heart attack is the recognition of symptoms such as chest pain. The ALERTS study provides an excellent comparison showing the efficacy of a Guardian Emergency Alarm compared to such recognition of symptoms.

Specifically, Figure 11.9-2 presents the distribution of time-to-door from Guardian detection of confirmed coronary occlusion to arrival at a medical facility. There were 52 such events, 34 arrivals in 27 Treatment subjects and 18 arrivals in 17 control subjects. These data include subjects with and without reported symptoms.

There were only 5 late arrival events (>2 hrs) in 4 Treatment subjects as compared with 18 late arrivals in 17 control subjects, most of which arrived days or weeks after the detected occlusion.

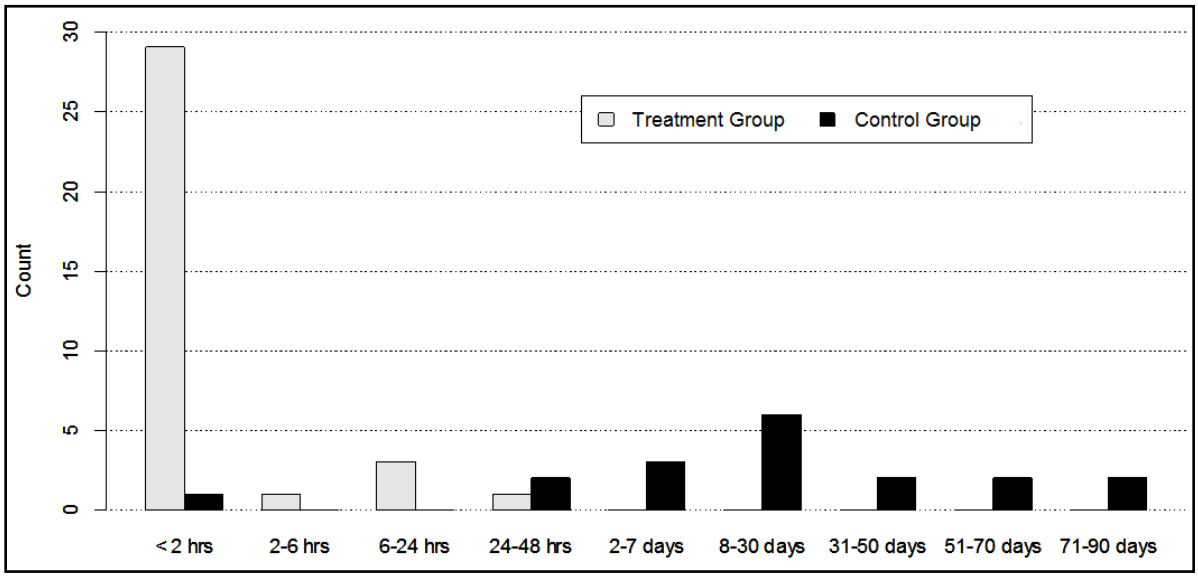

Figure 11.9-2 ALERTS distribution of subject arrival delays from Guardian detection for all confirmed thrombotic events during the 0-6 month randomized period.

Long delays (> 7 days) have also been reported in the literature. [8] Specifically Shelfer et al reported [9] with respect to myocardial infarctions, that "a substantial minority are accompanied by minimal or no discomfort. Consequently, many affected patients may not seek medical attention, and the diagnosis may be delayed for months or years." With 49.1% of ALERTS control subjects being diabetic, the occurrence of silent MI is not surprising. [10,11]

Figure 11.9-2 displays this data as the cumulative percent of arrivals vs. time with the 2 hour late arrival limit marked by the dashed line.

Figure 11.9-3 ALERTS cumulative distribution of subject arrival delays

The efficacy of patient alerting is clearly shown in Figure 2.5-3 as 85% (29/34) of Treatment subject arrivals compared to only 6% (1/18) of control subject arrivals were within 2 hours of detected, confirmed coronary occlusion. The statistically significant (posterior probability >

0.975) results for the treatment group having both reduced median time-to-door and reduced late arrivals >2 hours, follows in section 2.5.2.10 and also in the statisticians report in Appendix 2.1 as two of the reported secondary endpoints.

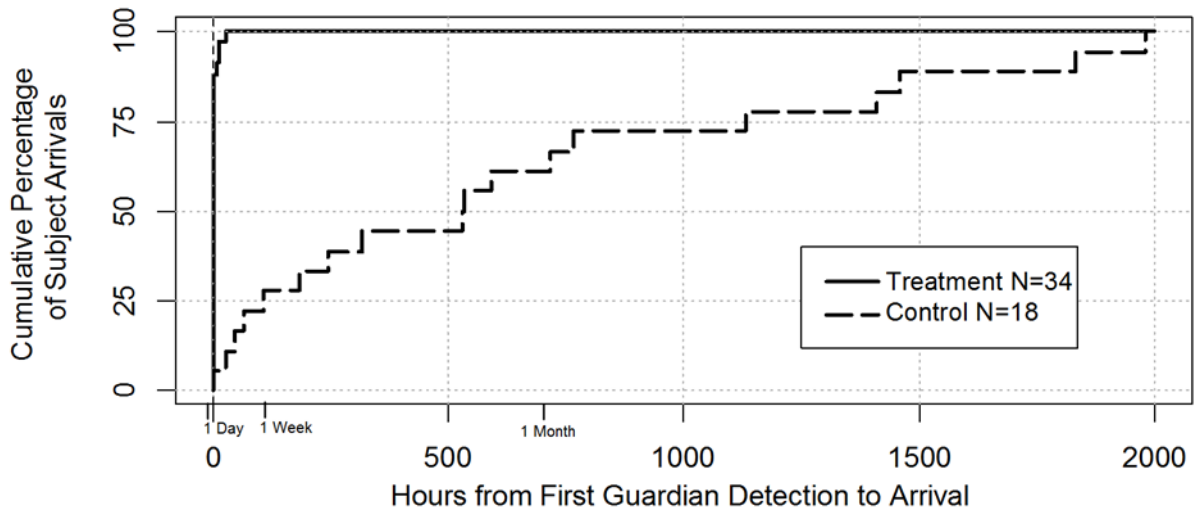

Figure 11.9-3 ALERTS cumulative distribution of all subject arrival delays

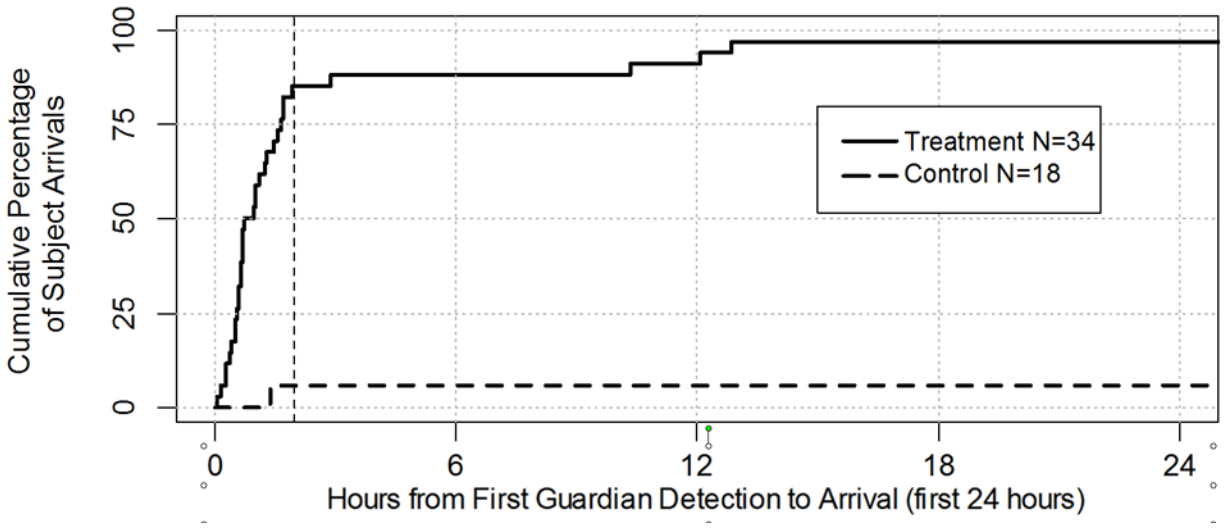

Figure 11.9-4 ALERTS cumulative distribution of all subject arrival delays(first 24 hours) following Guardian Alert/Detection for excessive ST shift

The efficacy of patient alerting is best shown in Figure11.9-4 as 85% (29/34) of Treatment subject arrivals compared to only 6% (1/18) of control subject arrivals were within 2 hours of detected, confirmed coronary occlusion. The recordings of ST shift events in the control group, allows the ALERTS study to capture, for the first time, the presentation patterns for patients with no symptoms or unrecognized symptoms. This control group behavior plus the clear effectiveness of alerting in getting Treatment group subjects in quickly is the most remarkable outcome of the ALERTS Clinical Study.

Clinical Benefit: Primary Efficacy Endpoint

The primary efficacy objective was to evaluate the effectiveness of the Guardian System in the detection of rapidly progressive ST-shift events indicative of a coronary occlusive event (usually thrombotic). This objective was evaluated over a relatively brief, 6-month follow-up period after randomization, and before the control group was crossed over to alerting. As specified, the primary efficacy endpoint was the composite of either (a) cardiac or unexplained death, (b) new Q-wave MI, or (c) time-to-door >2 hours for a confirmed thrombotic coronary occlusive event. Such a confirmed thrombotic event as defined in the study protocol is a detection of an ST-shift event followed by a positive standard of care test for coronary obstruction upon presentation at a medical facility.

In accordance with the ALERTS SAP and after adjudication of all events (by the ALERTS Group for Endpoint Adjudication (AGEA) Committee), angiograms (by the PERFUSE core lab) and all ECGs (by the eECG Core Laboratory at the Duke Clinical Research Institute using serial review of ECGs at randomization, 1, 3 and 6 months), the incidence of composite primary endpoint events and the posterior probability of a lower incidence in the treatment (alerting ON) group were computed. Results are shown in Table 11.9-2 using different look-back period windows for late arrival. A posterior probability at or above 0.975 is required to claim statistical significance.

Table 11.9-2 shows the primary efficacy endpoint posterior probability vs. look-back interval. The change in the number of control subjects meeting the primary endpoint from 21 to 29, is due

to the arrival of many of these control subjects more than 7 days after Guardian detection, as seen in Figure 11.9-2.

With all control subject late arrivals counted (90 day look-back), and using the original single baseline primary endpoint data from Table 11.9-2, the posterior probability of 0.974 strongly suggests a positive trend indicating that alerting reduces the number of primary endpoint events in the Treatment group.

Table 11.9-2 Bayesian posterior-probabilities for the composite primary objective using different "look-back" intervals

Line #	Look-back Window	Control Group (N=456)		Treatment Group (N=451)		*95% BCI (ON - OFF)*	*Posterior Prob* $Pr(R_{ON} < R_{OFF} \mid data)$
		N	Patients (%)	N	Patients (%)	*(Completers only)*	*(Completers only)*
1	*7-Day*	428	21 (4.9%)	423	16 (3.8%)	(-3.93%, 1.67%)	0.7856
2	*30-Day*	428	25 (5.8%)	423	16 (3.8%)	(-5.02%, 0.84%)	0.9177
3	*50-Day*	428	27 (6.3%)	423	16 (3.8%)	(-5.55%, 0.43%)	0.9527
4	*70-Day*	428	28 (6.5%)	423	16 (3.8%)	(-5.82%, 0.24%)	0.9644
5	*90-Day*	428	29 (6.8%)	423	16 (3.8%)	(-6.06%, 0.03%)	0.9740

The more accurate dual baseline analysis of the primary endpoint that corrected the new Q-Wave MI quality control issues discussed above, is shown in Table 11.9-3 from the statistician's report.

Table 11.9-3 Bayesian posterior-probabilities for the composite primary objective using different "look-back" intervals adjusted for Q-Wave quality control issues using dual baselines

Line #	Look-back Window	Control Group (N=456)		Treatment Group (N=451)		*95% BCI (ON - OFF)*	*Posterior Prob* $Pr(R_{ON} < R_{OFF} \mid data)$
		N	Patients (%)	N	Patients (%)	*Completers only)*	*(Completers only)*
1	*7-Day*	428	20 (4.7%)	423	13 (3.1%)	(-4.28%, 1.02%)	0.8833
2	*30-Day*	428	24 (5.6%)	423	13 (3.1%)	(-5.36%, 0.23%)	0.9637
3	*50-Day*	428	26 (6.1%)	423	13 (3.1%)	(-5.89%, -0.18%)	0.9812
4	*70-Day*	428	27 (6.3%)	423	13 (3.1%)	(-6.16%, -0.38%)	0.9870
5	*90-Day*	428	28 (6.5%)	423	13 (3.1%)	(-6.43%, -0.60%)	0.9908

The level of statistical significance of 0.975 is clearly surpassed when ECG Q-wave quality issues were reduced using the dual baseline ECG analysis shown in Table 11.9-3. The posterior probability exceeds **0.9908** with the 90 day look-back that includes all the late control subject arrivals shows that that this endpoint was highly statistically significant.

Secondary Endpoint: Reduction in Median Time to Arrival for All Subjects with "Confirmed Thrombotic Events"

Objective: To determine that the Guardian System reduces the time from the Guardian's ST shift detection to presentation at a medical facility for a confirmed thrombotic or ACS event for Treatment subjects when compared to control subjects.

Endpoint Result: The median time from Guardian detection to arrival at a medical facility was 51 minutes (0.85 hours) for treatment subjects who received alerts and 30 hours 8 minutes for control subjects. This was based on 43 events (which occurred in 35 subjects with arrival occurring within 7 days post detection for confirmed positive tests including positive 12 lead ECG, positive cardiac enzyme test, positive stress test, positive angiogram, or new Q-wave at 6 months). Control subjects had ST shifts detected and data captured but were not alerted, while Treatment subjects were alerted.

This difference as shown in Table 11.9-4 shows statistical significance (posterior probability > **0.9999**.

Table 11.9-4 Summary of Times from Detection to Arrival for Confirmed Thrombotic Event

Look-back Window	Group	Events (Subjects)	Mean ± SD (hours)	Min	Median (hours)	Max	Pr($\mu_T < \mu_C$ | data)
7-Day	OFF	9 (8)	52.33 ± 61.14	1.38	**30.13**	186.03	> 0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	**0.85**	26.63	
90-Day	OFF	18 (17)	664.48 ± 640.41	1.38	**532.71**	1980.44	> 0.9999
	ON	34 (27)	2.66 ± 5.30	0.05	**0.85**	26.63	

If all control late arrivals out to 90 days are included the treatment group remains unchanged at 0.85 hours while the control group median arrival time increases from 30 hours to 532.71 hours (22 days). The posterior probability remains above 0.9999 for all lookback windows including those at of 10, 30, 50 and 70 days.

Secondary Endpoint : Reduction of Late Arrivals for "Confirmed Thrombotic Events Where Late Arrivals are >2 hours Post Guardian ST Shift Detection.

Objective: To determine whether the Guardian System reduced the time-to-door (defined > 2 hours Emergency Alarm-to-arrival time, measured from the time the Guardian detected a rapidly progressive ST-Shift event to the time that the subject presented at a medical facility) for a confirmed thrombotic coronary event.

Endpoint Result: As one can see from Figures 11.9.2 and 11.9.3 the arrival pattern for control subjects and Treatment subjects are very different with most Treatment subjects arriving before 2 hours and most control subjects arriving more than 7 days after Guardian detection of a rapidly progressive ST shift event confirmed by one of the following: 12 lead ECG, cardiac enzymes, positive stress test, or angiography.

The posterior probability that the incidence of late arrivals (90 day maximum late arrival) is lower in the treatment (alerting ON) group is **0.9978**, indicating a reduction that is highly statistically significant.

This is based on the 21 subjects with late arrival events shown in Figure 1.5.2 with 17 subjects in the control group vs. 4 in the Treatment group arriving after 2 hours.

Other Endpoint: Echocardiographic Ejection Fraction at Discharge Following Recurrent Event

This endpoint captures the echocardiographic ejection fraction at discharge AFTER having a confirmed thrombotic occlusive event during the 6 month randomization period. Ejection fraction data was obtained from the case report forms. Only subjects with a confirmed thrombotic occlusive event and documented echocardiographic ejection fraction value at discharge were included in this analysis.

Please note that it is important to distinguish between subjects and events; a subject can have multiple events. The analysis lists 57 events (control (OFF) = 13; treatment (ON) = 44) which occurred in 44 subjects (control = 11; treatment = 33).

For the data presented the entry criteria required all of the following:

- an emergent medical facility visit
- a positive standard of care test result associated with the visit AND
- an associated EF measurement related to that emergent medical facility visit

Summary Table 11.9-5 below summarizes the individual LVEF data which reflects 57 events that occurred in 44 subjects.

Table 11.9-5 ALERTS Summary Statistics -- LVEF after discharge (%)							
Group	N	Mean ± SD	Min	Q1	Med	Q3	Max
Control	13	46.8 ± 14.7	30.0	30.0	53.0	55.0	73.0
Treatment	44	54.6 ± 10.1	18.0	48.0	55.0	61.5	70.0

* Note: Events in the Control group occurred in 11 subjects. Events in the Treatment group occurred in 33 subjects. All events are considered independent for statistical analysis of the means.

The hypothesis of interest is H: $\mu t > \mu c$, where μt and μc respectively represent the mean ejection fraction at discharge following an ACS event, in the treatment and control populations. The pre-specified analysis method is a Bayesian version of the t-test. Using this test, the posterior probability $P(\mu t > \mu c \mid data) = 0.9504$, with a 95% BCI for $(\mu t - \mu c) = (-1.63\%, 17.15\%)$. Because the posterior probability is < 0.975, there is not sufficient statistical evidence to conclude that the LVEF is higher at discharge in the treatment group than in the control group. In addition, in response to FDA request, sponsor undertook two additional, non pre-specified analyses of the data which included baseline LVEF values. The reason for assessing baselines as well as post-event LVEF is to determine whether the post-treatment difference was due to a difference of where the treatment and control group started (i.e. the difference found above was not already there at the start of the ALERTS trial).

In this analysis, the LVEF data were only considered for subjects who had both:

- Baseline LVEF assessment and
- LVEF assessment related to a medical facility visit with at least one positive standard of care test.

The baseline for any subject was counted only once in the calculation of the average baseline value. The data for this additional analysis is summarized in table 11.9-5-a below.

Table 11.9-5-a Echocardiographic Ejection Fraction at Baseline (N=44)							
Group	N	Mean ± SD	Min	Q1	Med	Q3	Max
Control	11	51.8 ± 9.8	30.0	45.0	55.0	57.5	65.0
Treatment	33	51.8 ± 10.0	20.0	47.0	50.0	55.0	75.0

*Note: Events in Control group occurred in 11 subjects. Events in Treatment group occurred in 33 subjects. Each subject contributes only 1 baseline measure to this analysis.

The above table shows that the treatment and control group conveniently started with the same average LVEF values. Summary statistics for the change from baseline are shown in the table below. Mean LVEF decreases by 2.8% in the control group and increases by 3.2% in the treatment group, nearly but not quite establishing statistical significance: $P(\mu t > \mu c \mid data) = 0.9737 (< 0.975)$, 95% BCI for $(\mu t > \mu c) = (–0.08\%, 11.93\%)$.

Table 11.9-5 -b Echocardiographic Ejection Fraction, Change From Baseline (N=57)							
Group	N	Mean ± SD	Min	Q1	Med	Q3	Max
Control	13	–2.8 ± 9.0	–15.0	-5.0	0.0	0.0	18.0
Treatment	44	3.2 ± 8.8	–25.0	–3.2	4.0	9.2	20.0

*Note: Change-from-baseline scores originate from 11 Control subjects and 33 Treatment subjects. All events are considered independent for statistical analysis of the means.

To answer the question of whether the treatment and control groups are different at baseline, the baselines were not repeated for subjects with multiple post-event EF measurements, so that all subjects are weighted equally. However, in order to assess whether one cohort changes more than another, while taking into account that some patients having repeated "post" measures, the

analysis relies upon a collection of change scores (i.e. mean of the paired differences), rather than comparing the mean baselines to the mean "post" LVEF" values.

Additional Benefits – ALERTS Study

The ALERTS study showed the Guardian system offers a number of important additional benefits not captured in the study endpoints, including: core lab confirmed alerts for silent ischemia in 38 subjects (23 thrombotic occlusions and 15 progressive coronary narrowing), confirmed presentation from alerts for arrhythmia and other medical conditions including transient heart block, bradycardia, tachycardia, atrial fibrillation, severe anemia, bundle branch block, hypokalemia, cardiomyopathy, and bigeminy. In addition, the treatment (alerting ON) group had 42.6% more cardiovascular medication adjustments and 60.9% more beta blocker medication adjustments compared to control (alerting OFF) group subjects during the 6 month randomized period.

Additional Benefits: Improvements in Quality of Life, AQOL Study

A patient's perspective on their health status has increasingly been recognized as an important and medically meaningful outcome. Measurement of health status and quality-of-life is increasingly being used in medicine and evaluated during assessment of coverage by payers [12] and large purchasers of healthcare [13] alike. It can predict long-term outcomes in patients with coronary heart disease [14]. Poor health status is related to a worsening of prognosis [15]. Healthstatus can also predict resource use and costs over time in patients with heart disease [16].

Health status can be measured through Quality of Life (QOL) instruments, which provide both quantitative and qualitative information related to patients' perception of how their disease and its treatment (e.g., stent, CABG, beta-blockers) affects them over time. For example, QOL can relate to a patient's ability to function along several dimensions (e.g., socially, physically, and emotionally). Treatment satisfaction, anxiety or depression levels may be measured in addition to the patient's overall feeling of well-being. An "instrument" refers to a constellation of items contained in a survey such as instructions to respondents, procedures for administration, scoring, interpretation of results, and other materials found in the respective user manuals

[17].

While the ALERTS study measured the clinical endpoints, another important aspect of care in these high risk patients is the subjects' own perception of their disease and how this perception affects their physical and mental health status over time. The AQOL study was designed and run as an independent study using ALERTS study subjects during the final 2 years of the ALERTS study from 2012 thru 2014.

Methods

The AQOL study serves to measure aspects of the ALERTS subject lives which are not captured elsewhere by ALERTS (e.g., anxiety, productivity, use of emergency-department resources). The AQOL study uses two well established QOL instruments known as the EuroQOL EQ-5D [18,19] and MacNew. [20–22] These have been used and validated to evaluate medical interventions including heart-related therapies. The AQOL study also includes a third custom QOL survey designed in collaboration with Dr. Neil Oldridge the designer of MacNew. This custom study, the AngelMed Quality of Life- Frequency of Emergency Department Usage (AMQOL-FEDU), was designed to measure changes in quality of life that are related specifically to Guardian heart-monitoring and alerting. All three surveys in the AQOL study were given to a subset of ALERTS subjects in order to prospectively examine changes in QOL by comparing the subject's quality of life during the year prior to implantation, to their quality of life at both 6 months ("Post-1") and 12 months ("Post-2") after their Guardian's alerting features were activated.

Two versions of three surveys for the AQOL study were used. Version 1 was given to both treatment and control subjects prior to implant. Version 2 was given to treatment subjects at 6 months (i.e., Post-1 time-point) and at 12 months (i.e., Post-2 time-point) after randomization which occurs 7-14 days after Guardian implant. Version 2 was given to control subjects at 12 and 18 months post-randomization since control subjects did not have alerts enabled for the first 6 months. The statistical analysis of the QOL data was performed using SPSS version [22] software. Repeated measures analysis of variance (ANOVA) was carried out, with significant main effects followed-

up using post-hoc t-tests. Chi-squared statistics were used to evaluate results that were reflected as percentage data.

Subject Enrollment

The study enrolled 157 subjects at 26 ALERTS study sites with 133 having Post-1 completion and 136 having Post-2 completion.

Results - Significant Improvements in Quality of Life

All three surveys showed a significant improvement in subject quality of life. Specifically:

EuroQOL measures quality of life using the EuroQOL Visual Analog Scale (VAS). This survey is non-specific to cardiac studies and is used to show QOL changes that are valid for inclusion in cost-analysis studies. The VAS results indicate an improvement in mean of paired differences of 4.6, at 6 ($p<0.01$) and 4.5 at 12 ($p<0.01$) months from 66.7 to 72.4 at 6 months and 72.3 at 12 months, post-implant. The 6 and 12-month EuroQOL VAS results indicate statistically significant benefit for mean of paired differences in quality of life.

MacNew is specific to assessing QOL changes in cardiac studies. The minimum clinically important difference is 0.5 MacNew points. Guardian MacNew global improvement is 0.6 at 6M and 0.5 at 1yr (means of paired differences between 6 and 12 months compared to pre-implant baseline, $p<0.0001$). Both 6 and 12-month MacNew results indicate clinically significant benefit in QOL.

The results from AMQOL-FEDU, showed that Guardian implanted subjects report extremely positive reactions to having the Guardian. Specifically, that the Guardian gives them “peace of mind.” and makes them feel safer with less anxiety and an overall improvement in quality of life. Table 11.9-6 summarizes the AMQOL-FEDU survey questions asked and the results.

Table 11.9-6 AMQOL-FEDU Survey Results

		6 Months				1 Year			
		Pos	Neutral	Neg	Efficiency Pos:Neg	Pos	Neutral	Neg	Efficiency Pos:Neg
1	More Control Since Alarms on	90%	5%	5%	20.0	88%	9%	4%	23.8
2	Safer Since Alarms on	91%	6%	3%	30.3	90%	5%	4%	20.5
3	QOL Improved	69%	24%	6%	11.5	69%	23%	8%	8.5
4	More Productive	48%	38%	14%	3.6	54%	30%	16%	3.3
5	Less Depressed	47%	27%	11%	4.2	43%	33%	10%	4.1
6	Slept Better	50%	29%	13%	3.9	50%	25%	15%	3.4
7	Less Anxiety	73%	16%	8%	9.7	71%	13%	11%	6.4
8	Less Anxiety (symptoms)	62%	13%	7%	9.1	51%	14%	13%	3.9
9	Worried Less About Overdoing It	62%	20%	13%	4.9	63%	20%	11%	5.7
10	Exercise	56%	21%	9%	6.3	63%	21%	9%	7.1
11	Sexual Activity	34%	17%	14%	2.4	34%	18%	9%	3.8
12	Average	**62%**	**20%**	**9%**	**6.7**	**61%**	**19%**	**10%**	**6.1**

Seventy percent of the subjects reported an improvement in quality of life at 6 months after Guardian alerting was enabled. This includes a large variety of improvements in QOL, such as success in going back to work, resuming normal day-to-day recreational activities as well as other health issues. The table also shows that the important improvements in quality of life at 6 months after alerting were sustained at one year.

Effectiveness

The ALERTS Clinical Study demonstrated that the AngelMed Guardian is effective and demonstrated that patients with confirmed thrombotic events will arrive more quickly in to a medical facility for standard of care evaluation. By itself, the occlusion-to-door median arrival time, following an alert, of under an hour dramatically surpasses the best results ever seen in any prior studies of patient symptom-to-door arrival times. The ALERTS Clinical Study for the first time enabled the demonstration of just how in-effective symptom recognition is in getting patients with confirmed thrombotic events to treatment quickly. In ALERTS the control subjects, representing the current real world response to coronary occlusion, present days and sometimes weeks after the coronary blockage might have been detected and treated.

The ALERTS Clinical Study demonstrated efficacy by meeting the primary effectiveness endpoint when all late arriving control patients were included and the dual baseline analysis was used to improve quality in the Q-wave MI component.

Additional efficacy was demonstrated by the treatment group compared to the control group having reduced time-to-door and late arrival secondary endpoints and higher left ventricular ejection fraction before discharge from a confirmed thrombotic event (an other pre-specified endpoint.

Safety

Safety was demonstrated in the ALERTS Clinical Study as the study met its primary safety endpoint by surpassing the required safety threshold of 90% freedom from system related complications. The final result was a 97.2% freedom from system related complications with no lasting morbidity.

Risk Benefit Analysis

The ALERTS Clinical Study demonstrated that the risks associated with the AngelMed Guardian are those associated with the implantation of the IMD and lead none of which had lasting morbidity.

On the other hand, the list of benefits to subjects is extensive.

- Statistically significant benefit was shown in favor of the treatment group for the dual baseline primary endpoint analyses, as well as a number of secondary and other endpoints including:
    - Reduction of death, new Q-wave MI or late arrival for confirmed thrombotic events using the 90 day lookback and dual baseline.
    - Reduction of median time-to-door for confirmed thrombotic events of 51 minutes for treatment subjects as compared to 22 days for control subjects
    - Reduction of late arrivals for treatment vs. control groups.
    - Higher left ventricular ejection fraction before discharge from a confirmed thrombotic event.

- Additional benefits not captured in the study endpoints, including:
    - core lab confirmed alerts for silent ischemia,
    - confirmed presentation from alerts for arrhythmia and other medical conditions,
    - improved beta-blocker dose management; and
    - statistically significant improvements in quality of life.

There is also clear evidence that the Guardian System can easily fit into the standard of care chest pain protocol used for the emergent evaluation of patients presenting with suspected AMI, adding value without introducing bias. The Guardian System is the first implanted device to provide either ST Segment monitoring or ST shift alerting in ambulatory subjects with advanced multi-vessel cardiac disease, and the ALERTS Clinical Study has shown that it can be done safely and effectively.

The Guardian device enables a new ability to detect a disease process with high morbidity and mortality at an earlier stage, where earlier intervention can change the disease process, making an important impact on both individual patients and public health.

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PANEL RECOMMENDATIONS (To be completed by FDA)

CDRH DESCISION (To be completed by FDA)

APPROVAL SPECIFICATION (To be completed by FDA)