SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Acute Coronary Syndrome Event Detector

Device Trade Name: AngelMed Guardian System

Device Procode: QBI

Applicant's Name and Address: Angel Medical Systems, Inc.
788 Shrewsbury Avenue, Suite 2200
Tinton Falls, New Jersey 07724

Date(s) of Panel Recommendation: March 16, 2016

Premarket Approval Application (PMA) Number: P150009

Date of FDA Notice of Approval: April 9, 2018

II. INDICATIONS FOR USE

The AngelMed Guardian System is an implantable cardiac monitor with patient alerting capability and an additional external alarm device. The Guardian System is indicated for use in patients who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events.

The Guardian System is indicated as an adjunct to patient recognized symptoms. The Guardian System detects potential ongoing ACS events, characterized by sustained ST segment changes, and alerts the patient to seek medical attention for those potential ACS events.

A Guardian System alert is a more accurate predictor of ACS events when compared to patient recognized symptoms alone and demonstrates a reduced rate over time of patient presentations without ACS events (false positives) when compared to patient recognized symptoms alone.

In the absence of symptoms, the Guardian System may identify asymptomatic ACS events and prompt the patient to seek medical attention.

III. CONTRAINDICATIONS

The AngelMed Guardian System should not be implanted in:

1. Patients with cognitive impairment that would prevent recognition of alarms
2. Patients who cannot feel the vibration from the IMD

3. Patients with implanted pacemaker, implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) devices
4. Patients where a pacemaker lead cannot be placed safely

IV. WARNINGS AND PRECAUTIONS

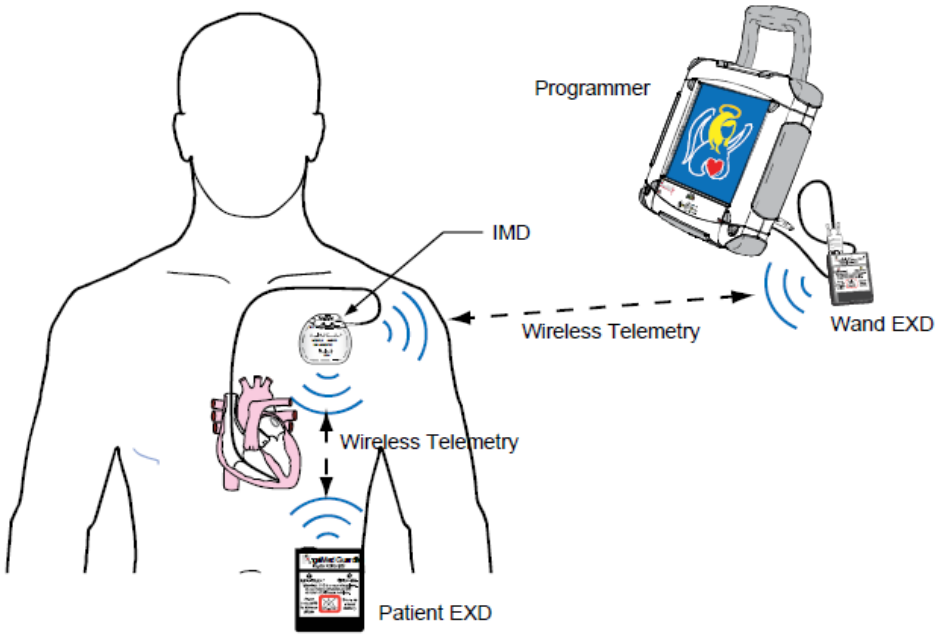
The warnings and precautions can be found in the AngelMed Guardian System labeling.

V. DEVICE DESCRIPTION

The AngelMed Guardian System consists of three (3) main components which are shown in Figure 1 below and described in further detail below:

1. Implantable Medical Device (IMD)
2. External Device (EXD)
3. A Programmer

Figure 1 - Guardian System Component Diagram



Implantable Medical Device (IMD)

The IMD is implanted in a left pectoral subcutaneous pocket, similar to a permanent pacemaker, and connects to a market approved, IS-1, 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.

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.

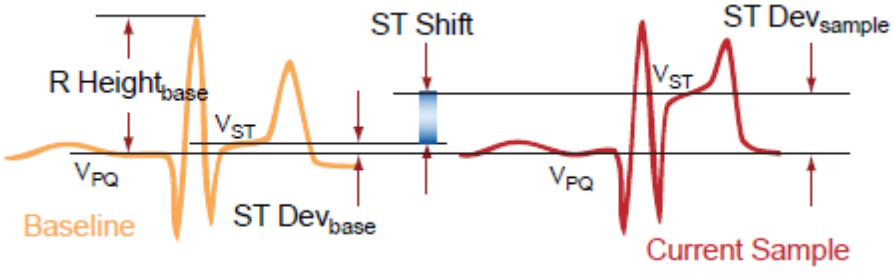
Programmer

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.

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, measured between the tip of the lead and the IMD 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 (6) shifted beats to declare the electrogram shifted. If three (3) 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 vibratory and auditory pattern 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no alternatives to the proposed device for near real-time, outpatient monitoring for ACS events. Current patients at risk for ACS must rely only on patient recognized symptoms to prompt them to seek medical attention.

VII. MARKETING HISTORY

The AngelMed Guardian System has received market approval in the following entities:

Approving Entity	Date of Market Approval
European Union (CE Mark)	February 24, 2010
Brazil	November 11, 2013

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the system.

- Air embolism
- Allergic reaction
- Bleeding
- Body rejection phenomena including local tissue reaction
- Cardiac dissection
- Cardiac perforation
- Cardiac tamponade
- Chronic nerve damage
- Damage to the vessel at the catheter insertion site
- Death
- Device failure resulting in removal or replacement
- Endocarditis
- Erosion
- Excessive fibrotic tissue growth
- Extrusion
- False negative (FN) device alarms
- False positive (FP) device alarms
- Fluid accumulation
- Formation of fibrotic tissue, local tissue reaction
- Formation of hematoma or cysts
- Induced ventricular ectopy
- Infection
- Ischemia
- Keloid formation
- Lead abrasion and discontinuity
- Lead migration/dislodgment
- Loss of sensing due to dislodgement or mechanical malfunction of the lead

- Myocardial damage
- Myocardial irritability
- Nausea and vomiting
- Pain in shoulder or arm
- Palpitations
- Pericardial effusion
- Pericardial rub
- Pneumothorax
- Procedure related, random component failure
- Shunting current or insulating myocardium during defibrillation
- Stroke from a clot being disloged by the catheter
- Thromboemboli
- Thrombosis
- Valve damage
- Vascular complications, which may require vessel repair
- Vein wall rupture
- Venous occlusion
- Venous perforation
- Ventricular fibrillation
- Visibile bump at implant site that may cause discomfort under clothing

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Table 1 below details the non-clinical testing performed on the device. As described in Section V above there are three (3) major components: Implantable Medical Device (IMD), External Device (EXD), and Programmer (PROG) and testing denoted with IMD, EXD, or PROG refers to testing that was only performed on that specific component.

Table 1. Summary of Non-Clinical Testing

Electromechanical Environmental Effects			
Test	**Purpose**	**Acceptance Criteria**	**Results**
EAS (Electromagnetic Article Surveillance) Tag Deactivator Metal Detector RFID Microbial Challenge Tensile Burst Dye	To assess the Electromagnetic Environmental Effects on the Guardian system	ASTM F1608	Pass
FCC Certification			
Test	**Purpose**	**Acceptance Criteria**	**Results**

IMD: Occupied Bandwidth Radiated Emissions Frequency Stability over temperature Radiated RF Immunity Conducted RF Immunity Electrostatic discharge (ESD) Immunity	To assess the compliance of the IMD with FCC requirements	ETSI EN 300 220-1: 2010 ETSI EN 300 220-2: 2010 ETSI EN 301 489-1: 2008 ETSI EN 301 489-27: 2004 ETSI EN 301 839-1: 2009 ETSI EN 301 839-2: 2009 IEC 60601-1-2:2007 FCC (47 CFR Part 95) EN45502	Pass
EXD: Occupied Bandwidth Radiated Emissions Frequency Stability over temperature Radiated RF Immunity Conducted RF Immunity Electrostatic discharge (ESD) Immunity	To assess the compliance of the EXD with FCC requirements	47 CFR (FCC) Part 95.628 47 CFR (FCC) Part 95.631 47 CFR (FCC) Part 95.633 47 CFR (FCC) Part 95.635 47 CFR (FCC) Part 95.639 47 CFR (FCC) Part 15.209 CISPR 16-1 (2003) ETSI EN 300 220, 2000 ETSI EN 301 839-1 ETSI EN 301 489-1, 2002 ETSI EN 301 489-27 IEC 60601-1-2: 2001 IEC 61000-4-2, 2002 IEC 61000-4-3, 2002 IEC 61000-4-6, 2003	Pass
PROG: Radiated Emissions Conducted Emissions Electromagnetic Compatibility Radiated RF Immunity Conducted RF Immunity Electrostatic discharge (ESD) Immunity Surges Immunity Electrical fast transients and bursts Immunity Voltage dips, short interruptions, and voltage variations on power supply input lines Immunity Magnetic fields Immunity	To assess the compliance of the PROG with FCC requirements	IEC 60601-1-2:2007/IEC CISPR:2006 IEC 60601-1-2:2007 clause 17 IEC 60601-1-2:2007 clause 6.2	Pass

Cellular Phone Interference			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Analog (AMPS) method CDMA (Cellular) CDMA (PCS) TDMA - 50Hz (Cellular) TDMA - 50Hz (PCS) TDMA - 217Hz (GSM-850) TDMA - 217Hz (GSM-900) TDMA - 217Hz (DCS-1800) TDMA - 217Hz (DCS-1900)	To assess the effects of various cellular phone types on the Guardian system	11 possible interference levels/ categorizations were pre-defined and measured	Pass: Only the following interference levels were observed: - 'No interaction' - 'Minor Interference; does not impair normal IMD operation

Mechanical & Environmental			
Test	**Purpose**	**Acceptance Criteria**	**Results**
IMD: Weight Dimensions AMSG3 Vibration Characterization Testing Hermeticity Radiopaque identification Operating/storage temperature/humidity Temperature shock Operating/storage atmospheric pressure Drop (free fall) Transportation vibration Operational vibration Header torque testing Header push-off testing AMSG3 Header Insulation Testing AMSG3 Amplifier/Filter Characterizations	To assess the compliance of the IMD with various Mechanical and Environmental requirements	EN 45502-1:1998 ISO 5841-3:2007 BS EN 50077:1993	Pass

EXD: Weight Dimensions Operating/storage temperature/humidity Temperature shock Excessive Temperatures Operating/storage atmospheric pressure Drop (free fall) Transportation vibration Operational vibration	To assess the compliance of the EXD with various Mechanical and Environmental requirements	EN 45502-1:1998 IEC 60601-1: 2001	Pass
PROG: Transport/Storage Operating Excessive Temperature Strength/ Rough Handling Sinusoidal Vibration (sweep) Random Vibration Bump Free Fall from 75cm Usage Temperature Storage Temperature Humidity	To assess the compliance of the PROG with various Mechanical and Environmental requirements	IEC 60601-1:2005 clause 7.9.3 IEC 60601-1:2005 clause 11.1.1 IEC 60601-1:2005 clause 11.1 IEC 60601-1:2005 clause 15.3 EN 13718-1 4.7.2 Annex A.1 EN 60068-2-6 EN 60068-2-64 EN 60068-2-29 EN 60068-2-32 EN 13718-1 4.2.2 EN 13718-1 4.7.3 EN 60601-1:1990 clauses 10 and 44	Pass

Electrical Safety			
Test	**Purpose**	**Acceptance Criteria**	**Results**
IMD: Amplifier Input Protection Electric Shock Defibrillation Ultrasound Radiated Immunity Energy Delivered Energy Extracted	To assess the compliance of the IMD with electrical safety standards	EN 45502-1:1998	Pass
EXD: Electric Shock Energy Delivered Energy Extracted	To assess the compliance of the EXD with electrical safety standards	IEC 60601-1: 2001	Pass
PROG: Electric Shock Leak Current	To assess the compliance of the PROG with electrical safety standards	IEC 60601-1:2005 clauses 6.1, 8.1, and 8.5	Pass
Human Factors			
Test	**Purpose**	**Acceptance Criteria**	**Results**
Guardian System Risk Assessment	To identify potential hazards of the Guardian system along with the possible causes, mitigation, and risk assessment.	No issues found	Pass
Guardian System Human Factors Risk Identification	To identify the Human Factors use issues associated with the Guardian system components	No issues found	Pass
Guardian Task Analysis And Use Error Risk Assessment	To examine the potential use error and mitigation for all anticipated patient-and clinician-related tasks.	No issues found	Pass

Vibratory And Auditory Alarm Characteristics	To finalize the vibration and frequency characteristics alarm and alert patterns	No issues found	Pass
Learning and Memory of Emergency Alarms and See Doctor Alerts	To evaluate patients' ability to learn and recall the appropriate responses alarms and alerts	No issues found	Pass
IMD AMSG3 Vibratory Alarm Characteristics	To verify that patients can readily sense the vibration generated by the AMSG3 vibratory motor	No issues found	Pass
Usability Test of the AngelMed Patient Manual	To evaluate the usability of the Patient Manual	No issues found	Pass
Guardian Programmer Usability Audit	to evaluate the usability of Programmer	No issues found	Pass

*Human factors testing was conducted by moving through typical device use cases and observing any potential safety issues that could result from use by an operator. The acceptance criteria for passing is that no issues have been obseverved. Note: If issues were observed then that result was typically fed back into the design of the device so that the use issue will not occur when the testing is re-performed.

Packaging			
Test	**Purpose**	**Acceptance Criteria**	**Results**
IMD: Package Test Process Qualification Product Performance Qualification	To assess the suitability of the IMD packaging	AAMI/ANSI/ISO 11607	Pass
EXD: Package Test	To assess the suitability of the EXD packaging	ASTM D-4169	Pass
PROG: Package Test	To assess the suitability of the PROG packaging	EN 13718-1	Pass

The engineering study results demonstrated the following conclusions:

- Performs as expected in the presence of systems commonly found in places like retail stores, libraries, and airports (e.g., RFID, EAS Systems, Tag Deactivator Systems, and security metal detectors)
- Passes FCC Certification tests: radiated emissions, conducted emissions, radiated RF immunity and RF safety levels
- Performs acceptably in the presence of commonly used cellular technologies
- Complies with all applicable mechanical and environmental requirements and international standards
- Complies with all applicable electrical requirements and electrical safety standards
- Complies with all applicable packaging standards

Table 2 below summarizes the biocompatibility testing performed to demonstrate that the system will not have an adverse effect on tissues it comes into contact with while implanted. The results for all tests indicated the device met the acceptance criteria of the referenced standards.

Table 2. Biocompatibility

Test	Standard	Result	Analysis Type
Genotoxicity: Ames Test (Solids)	ISO 10993-3:2003 ISO 10993-12:2007	Non-mutagenic	Attribute -- Third Party Testing
Genotoxicity: In Vivo Mouse Micronucleus	ISO 10993-3:2003 ISO 10993-12:2007	Non-mutagenic	Attribute -- Third Party Testing
Genotoxicity: Mouse Lymphoma, per Extract	ISO 10993-3:2003 ISO 10993-12:2007	Non-mutagenic	Attribute -- Third Party Testing
Cytotoxicity: MEM Elution	ISO 10993-1:2009 ISO 10993-5:2009 ISO 10993-12:2007	Non-cytotoxic	Attribute -- Third Party Testing
Sensitization: Magnusson-Kligman Method	ISO 10993-10:2010 ISO 10993-12:2007	Non-sensitive	Attribute -- Third Party Testing
Irritation: Intracutaneous Toxicity (ISO)	ISO 10993-10:2010 ISO 10993-12:2007	Non-irritant	Attribute -- Third Party Testing
Systemic Toxicity: Systemic Injection (ISO)	ISO 10993-11:2006 ISO 10993-12:2007	Non-toxic	Attribute -- Third Party Testing
Systemic Toxicity: Material Mediated Pyrogen	ISO 10993-11:2006 ISO 10993-12:2007	Non-pyrogenic	Attribute -- Third Party Testing

Test	Standard	Result	Analysis Type
Subacute/ Subchronic Toxicity - 14 Day/14 Dose Exposure test	ISO 10993-11:2006	Negative-toxicity	Attribute -- Third Party Testing
Implant Study	ISO 10993-6:2007/ (R) 2010	Non-irritant	Attribute -- Third Party Testing

The following US and International standards were used in the development and testing of the Guardian System.

Table 3. US and International Standards

EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer (Clauses 8.1, 10.4, 19.3)
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
ISO 14155-1:2011	Clinical investigation of medical devices for human subjects -- Part 1: General requirements
ISO 14155-2:2003	Clinical investigation of medical devices for human subjects -- Part 2: Clinical investigation plans
ISO 60601-1:2005	Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
IEC 62304:2006	Medical device software – Software life cycle processes
IEC 60812:2006	Analysis techniques for system reliability – Procedure for failure mode and effects analysis (FMEA)
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
IEC 62304:2006	Medical device software – Software life cycle processes
IEC 60812:2006	Analysis techniques for system reliability – Procedure for failure mode and effects analysis (FMEA)
IEC 60601-1-1:2000	General requirements for safety – Collateral standard: Safety requirements for medical electrical systems
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
IEC 60601-1-1:2000	General requirements for safety – Collateral standard: Safety requirements for medical electrical systems

ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
ISO 14155-1:2011	Clinical investigation of medical devices for human subjects -- Part 1: General requirements
ISO 11607-1:2006	Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems
ISO 11607-2:2006	Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes
ASTM F1980 – 07	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
IEC 62304:2006	Medical device software – Software life cycle processes
IEC 60812:2006	Analysis techniques for system reliability – Procedure for failure mode and effects analysis (FMEA)
IEC 60601-1-1:2000	General requirements for safety – Collateral standard: Safety requirements for medical electrical systems
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
ISO 14155-1:2011	Clinical investigation of medical devices for human subjects -- Part 1: General requirements
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
IEC 60601-1-1:2000	General requirements for safety – Collateral standard: Safety requirements for medical electrical systems
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer

ISO 11135-1:2007	Sterilization of health care products. Ethylene oxide. Requirements for development, validation and routine control of a sterilization process for medical devices
EN 550:1994	Sterilization of medical devices. Validation and routine control of ethylene oxide sterilization
EN 556:2001	Sterilization of medical devices. Requirements for medical devices to be designated "STERILE". Requirements for terminally sterilized medical devices
EN 868-1:1997	Packaging materials and systems for medical devices which are to be sterilized. General requirements and test methods
ISO 11607-1:2006	Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems
ISO 11607-2:2006	Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
ISO 11737-1:2006	Sterilization of medical devices -- Microbiological methods -- Part 1: Determination of a population of microorganisms on products
ISO 11737-2:2009	Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the validation of a sterilization process
ISO 11737-3:2004	Sterilization of medical devices -- Microbiological methods -- Part 3: Guidance on evaluation and interpretation of bioburden data
ISO 14937:2009	Sterilization of health care products -- General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices
ISO 14644-1:1999	Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness
ISO 14644-2:2000	Cleanrooms and associated controlled environments -- Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
EN 45502-1:1997	Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer
EN 1041:2008	Information supplied by the manufacturer with medical devices
EN 980:2008	Graphical symbols for use in the labeling of medical devices
ISO 14971:2007	Medical devices -- Application of risk management to medical devices
ISO 13485:2003	Medical devices - Quality management systems - Requirements for regulatory purposes
ISO/TR 14969:2004	Medical devices -- Quality management systems -- Guidance on the application of ISO 13485: 2003
ISO 7000:2004	Graphical symbols for use on equipment -- Index and synopsis
TIR 60878	Graphical symbols for electrical equipment in medical practice

ISO 15223:2000/Amd 1:2001	Medical devices -- Symbols to be used with medical device labels, labeling and information to be supplied
ISO 15223-1:2012	Medical devices – Symbols to be used with medical device labels, labeling, and information to be supplied – Part1: General requirements

B. Animal Studies

A formal Good Laboratory Practice (GLP) animal study was conducted in 11 pigs implanted with an RV apical pacemaker lead and the AngelMed Guardian IMD implant. Five (5) pigs were implanted for long-term safety evaluation. Each of the remaining six (6) pigs then received two (2) copper stents in one of the three (3) 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 Left Anterior Descending, Left Circumflex, and Right Coronary Artery coronary arteries resulting from a coronary blood clot.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant conducted the ALERTS Clinical Study to establish a reasonable assurance of safety and effectiveness of the AngelMed Guardian System to monitor a patients' intracardiac electrogram for ST segment shifts indicating coronary ischemia in the US under IDE # G060259. The following two (2) major analyses of data collected from ALERTS study patients were presented to FDA and are summarized below.

a. A pre-specified, randomized analysis; and
b. An Additional Analysis of ALERTS ED Visits

The approval of this PMA is based on the clinical data presented below.

A. Study Design

Randomized Analysis/Original Follow-Up

The ALERTS Clinical Study was a Bayesian adaptive, randomized (1:1) controlled trial in which patients in the Alarm ON group had the device's alerts enabled while patients in the Alarm OFF group had those alerts disabled initially.

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 ALARMS ON (Treatment) and ALARMS OFF (Control) groups. Patients in both groups were implanted with a Guardian System device and those in the

ALARMS ON group had the Guardian alarms activated at the time of randomization (7-14 days post implantation) while those in the ALARMS OFF group had their alarms deactivated and devices placed in a monitoring mode for the first 6 months for randomized comparison between the two (2) groups. After the 6 month randomized period the alarms in all trial devices were activated and patients were followed per the IDE protocol.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ALERTS study was limited to patients who met the following inclusion criteria:

   a. Advanced multi-vessel Cardiac Disease
   b. An index ACS event (e.g., Myocardial Infarction (MI), Unstable Angina, or Coronary Artery Bypass Graft (CABG) within 6 months of enrollment)
   c. Additional risk factors/co-morbidities (diabetes, TIMI risk score≥3, or renal insufficiency)
   d. Lives in a geographic area in close proximity (within 60 minutes by Emergency Medical Services) to any hospital that can treat Acute Myocardial Infarction
   e. Greater than 21 years of age
   f. Women of childbearing age must have a negative pregnancy test or confirmation of one of the following:

      i. Post-menopausal or amenorrheic during the past year
      ii. Surgical sterilization
      iii. Use of effective contraceptive method

   Patients were not permitted to enroll in the ALERTS study if they met any of the following exclusion criteria:

   a. 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.).
   b. 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).
   c. 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.
   d. Subject cannot feel the IMD vibration when placed on top of the skin on the left pectoral side of the chest.
   e. Subject has recurrent or persistent atrial fibrillation.

f. Subject has recurrent or persistent non-sinus cardiac rhythm, second or third degree atrioventricular blocks, QRS duration greater than 120 msec, Benign Early Repolarization (BER), or Brugada Syndrome.
g. Subject has left ventricular hypertrophy evidenced by ECG criteria.
h. 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 device placed in a left pectoral location or left side PICC line.
i. 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.
j. There is evidence of unresolved infection (fever > 38^{o} C and/or leukocytosis > 15,000).
k. Subject has history of bleeding disorders or severe coagulopathy (platelets < 100,000 plts/ml; APTT or PT > 1.3 x reference range).
l. Subject has had a hemorrhagic stroke or transient ischemic attack (TIA) in the past 6 months.
m. 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.
n. 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.
o. 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.
p. Subject has experienced gastro-intestinal hemorrhage in the past 6 months.
q. Subject has any situation in which the use of aspirin is contraindicated for at least 6 months.
r. Subject has epilepsy.
s. Subject has known severe allergies (e.g., peanut, bee sting, etc.).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 7-14 days and 1, 3, and 6 months and every 6 months after that postoperatively. It should be noted that the effectiveness evaluation for the new clinical analysis plan does not rely on data from scheduled visits but only on adjudication of emergent visits in the Emergency Department (ED).

Preoperatively, all patients were seen in clinic and a baseline 12-lead ECG was

taken. Postoperatively, the objective parameters measured during the study included any ACS standard of care testing that was performed during an emergent ED visit. Adverse events and complications were recorded at all pre-specified follow-up examinations noted above.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

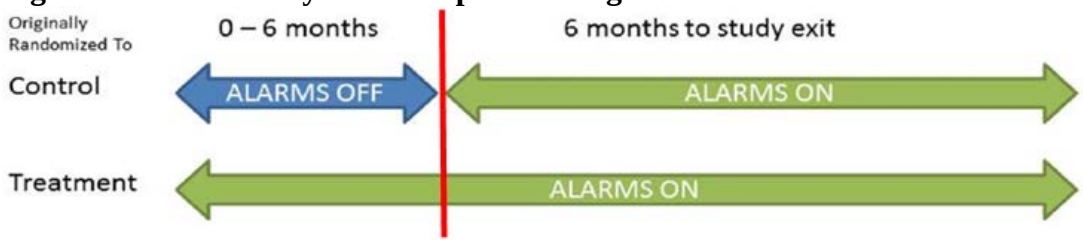
The following were the primary endpoints for the ALERTS Clinical Study:

a. Primary Safety Endpoint
   i. Proportion of subjects free from system-related complications is greater than 90%.
b. Composite Primary Effectiveness Endpoint (ALARM ON < ALARM OFF)
   i. Cardiac/Unexplained Death
   ii. New Q-Wave MI (QWMI)
   iii. Late Arrival – Time-to-door (time between device alarm and medical presentation) > 2 Hours for an ACS Event (confirmed by ECG, Stress test, Angiogram, or Enzymes)

Additional Analysis of ALERTS ED Visits/Original and Extended Follow-Up

After presentation of the ALERTS Clinical Study/Original Follow-Up to an Advisory Panel, FDA engaged the applicant to create a new clinical analysis plan that would include events in ALERTS patients from both the randomized and non-randomized period of the trial. This additional clinical analysis of ALERTS patient follow-up was a retrospective study of all ED visits for study patients that met specific criteria from the entirety of the follow up from the ALERTS IDE study; therefore, the additional analysis included data that were collected outside the prespecified randomization period and thus were not reviewed under the original PMA or presented to the Advisory Panel. The new clinical analysis compares device functionality related to ED visits for patients whose device alarm initiated (with or without symptoms) the visit (ALARMS ON,) shown in the green in Figure 3 below, and patients whose device alarms were inactive and whom presented due to symptoms (ALARMS OFF,) shown in blue in Figure 3 below.

Figure 3 - Guardian System Component Diagram



For a study subject's ED visit to be included in the analysis at least one of the following standard of care tests for ACS had to have been performed on the study subject:

a. 12-Lead ECG;
b. Cardiac Enzymes;
c. Stress Test;
d. Angiography

Note: *It was not necessary for an ED visit in the ALARMS OFF group to have been initiated by symptoms typically associated with cardiac events to be included in the analysis.*

Figure 3 shows how the assignment of the Control and Treatment groups during the 6-month randomization period relates to the ALARMS OFF and ALARMS ON groups used by the new clinical analysis protocol. In the post-randomization period the Control group patients were re-categorized into the ALARMS ON group."

Each ED visit was evaluated by an independent Clinical Events Committee (CEC) based on pre-specified criteria and adjudicated as an ACS event based on predetermined criteria or a false positive presentation to the ED. The ALARMS ON patients represent the treatment group for this new clinical analysis and were compared to the ALARMS OFF patients which represent the control group for both Positive Predictive Value (PPV) and False Positive Rate (FPR) using frequentist statistics.

The database for the Additional Analysis of ALERTS ED Visits was collected from ALERTS study initiation through May 2016 and included the 907 implanted and randomized patients.

1. Clinical Inclusion and Exclusion Criteria

   The Inclusion and Exclusion Criteria did not change from the randomized analysis. See above.

2. Follow-up Schedule

   All patients that were included in the Additional Analysis of ED Visits/Extended Follow-Up followed the follow-up schedule noted above for the pre-specified ALERTS/Original Follow-Up study. It should be noted that this new clinical analysis focused on data collected during emergent visits to the ED and not on data collected during regularly scheduled follow-up visits that occurred every 6 months.

3. Clinical Endpoints

With regards to safety, the following data was collected in the Additional Analysis of ALERTS ED Visits for the entire ALERTS study follow up period independent of randomized group:

a. System-Related Complication Rate
b. Replacement Implant System-Related Complication Rate
c. Explant Procedure System-Related Complication Rate
d. All Cause Death
e. Cardiac Death

No formal statistical tests were performed on the collected safety data for the Additional Analysis of ALERTS ED Visits.

With regards to effectiveness, the co-primary endpoints were analyzed as follows:

a. PPV – Superiority
   i. H_O: $PPV_{Alarm\ ON} \leq PPV_{Alarm\ OFF}$
   ii. H_A: $PPV_{Alarm\ ON} > PPV_{Alarm\ OFF}$
b. FPR – Non-Inferiority
   i. H_O: $\beta \geq 1.50$
   ii. H_A: $\beta < 1.50$
   iii. Where β is a regression coefficient used to approximate $\frac{FPR(Alarm\ ON)}{FPR(Alarm\ OFF)}$

B. Accountability of PMA Cohort

At the time of database lock, of 1020 patients enrolled in the PMA study, 88.9% (907) patients were available for analysis. Figures 4 and 5 below depicts the accountability of patients throughout the follow up of the entire ALERTS study.

Figure 4 - Patient Accountability during Randomized Period of the ALERTS Study/Original Follow-up

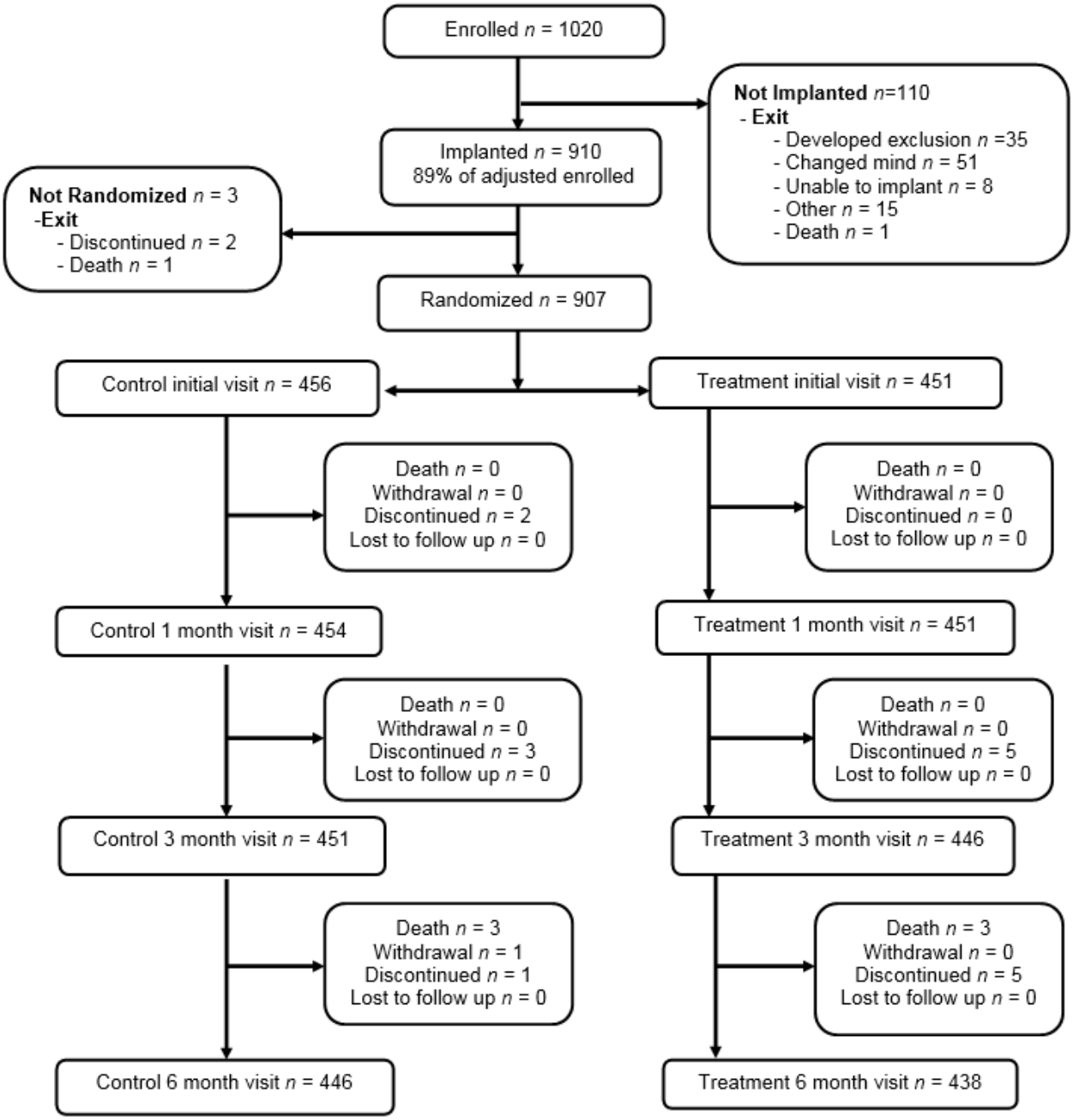
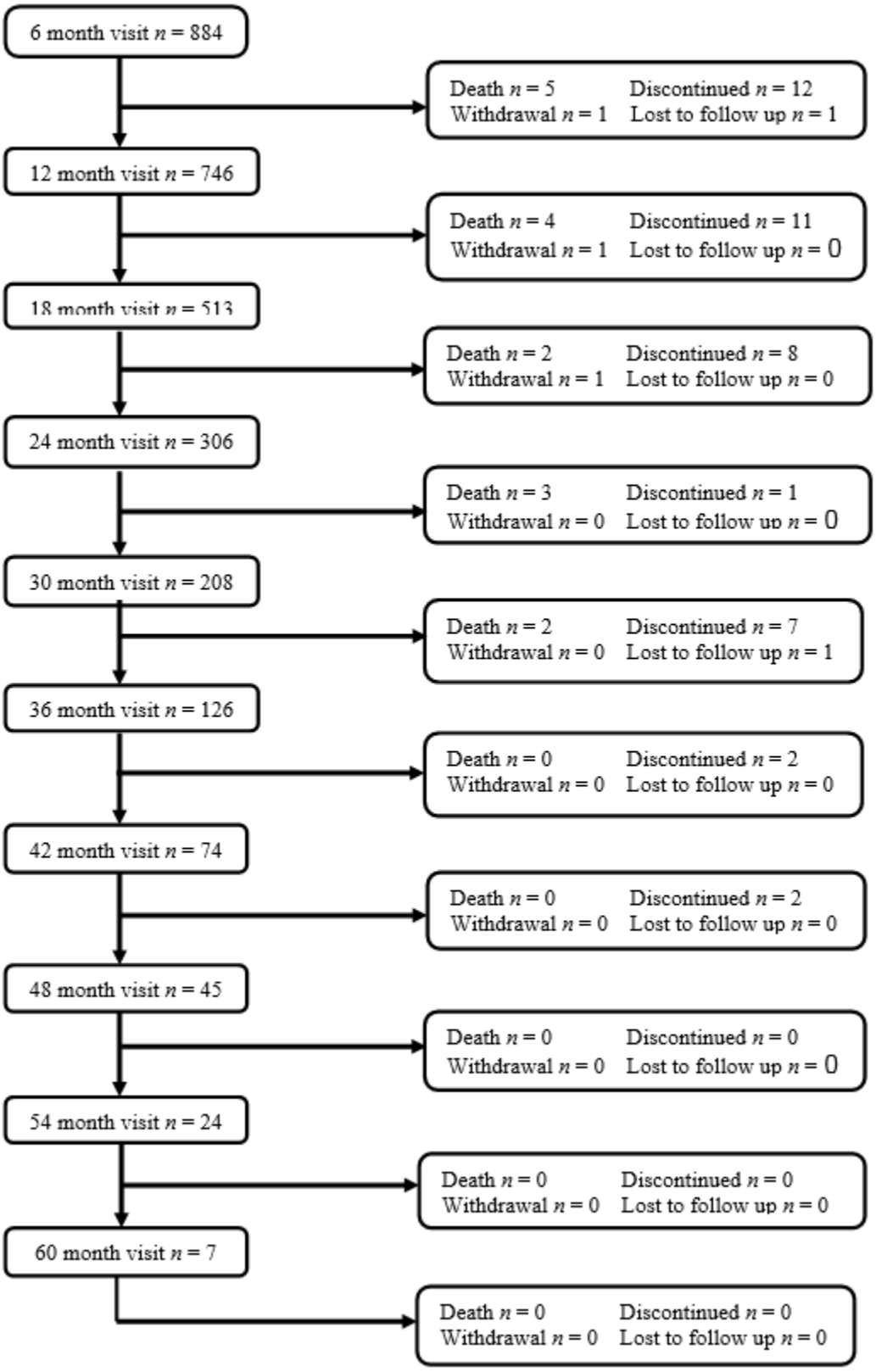


Figure 5 - Patient Accountability after the Randomized Period of the ALERTS Study/Extended Follow-up



Note: This patient accountability represents the number of patients who had reached each time point at the time of database lock. All patients were followed through the IDE until study exit.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a cardiac device study performed in the US. A summary of those characteristics is provided with respect to their original randomized groups in Table 4 below. Note that all ALARMS OFF patients crossed over to the ALARMS ON group at the 6-month follow-up visit.

Table 4: ALERTS Study Subject Demographics

Characteristic	ALARMS OFF (Control) Group (N=456)		ALARMS 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	137 (30.4%)	(-9.4%, 2.7%)
Race/Ethnicity	456		451		
- American Indian		1 (0.2%)		0 (0.0%)	(-1.0%, 0.5%)
- Asian/Pacific Islander		2 (0.4%)		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 (24.8%)		109 (24.2%)	(-6.2%, 5.0%)
- NSTEMI		127 (27.9%)		126 (27.9%)	(-5.7%, 5.9%)
- Unstable Angina		199 (43.6%)		199 (44.1%)	(-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		

Characteristic	ALARMS OFF (Control) Group (N=456)		ALARMS ON (Treatment) Group (N=451)		Difference (ON – OFF)
	N	Mean ± S.D. or N (%)	N	Mean ± S.D. or N (%)	95% BCI
- 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)
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%)

D. Safety and Effectiveness Results

Randomized Analysis/Original Follow-up

The key results of the randomized analyses for the ALERTS Clinical Study are presented below. For additional information on these results please refer to the Executive Summary for the relevant Advisory Panel meeting (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM490460.pdf).

1. Safety Results

Thirty-one (31) system-related complication events as defined for the primary safety endpoint were observed during the randomized period of the study and are presented in Table 5 below. The primary safety endpoint for the randomized period of the trial was met with a posterior probability of >0.9999 which was above the significance threshold of 0.954.

Table 5: System-Related Complications – Original Follow-Up

Complication	# of Events (%)
Cardiac Perforation	2 (0.22%)
Erosion	3 (0.33%)
Infection	11 (1.21%)
Lead migration/dislodgement	4 (0.44%)
Device Malfunction	2 (0.22%)
Lead Malfunction	1 (0.11%)
Loss of sensing due to dislodgement or malfunction of the lead	2 (0.22%)
Pain at or near the pocket site	5 (0.55%)
Visible bump where implanted in the chest	1 (0.11%)

These 31 events were observed in 30 patients resulting in an overall complication rate of 3.30% from the randomized period of the study.

2. Effectiveness Results

Table 6 below presents the results from the primary effectiveness endpoint for the randomized analysis of the ALERTS clinical study.

Table 6: ALERTS Randomized Effectiveness Analysis – Original Follow-Up

		ALARMS OFF (N=456)		ALARMS ON (N=451)		
		N	Pts (%)	N	Pts (%)	
Component – Cardiac or Unexplained Death						**Posterior Probability***
		447	1 (0.2%)	441	3 (0.7%)	
Component – New QWMI (dual baseline analysis)						
		427	13 (3.0%)	420	7 (1.7%)	
Component – Time-to-door > 2 hours						
Look-back Window	**7-Day**	446	8 (1.8%)	439	4 (0.9%)	
	90-Day	446	17 (3.8%)	439	4 (0.9%)	
Composite Primary Endpoint Events (with dual baseline analysis)**						
Look-back Window	**7-Day**	428	20 (4.7%)	423	13 (3.1%)	0.8833
	90-Day	428	28 (6.5%)	423	13 (3.1%)	0.9908

*The significance threshold for the posterior probabilities of event reduction is 0.983 for the primary effectiveness endpoint.

**The dual baseline analysis incorporated both pre-implant and randomization ECGs as baseline to more accurately identify new, persistent Q-waves observed during the study

Additional Analysis of ALERTS ED Visits/Original and Extended Follow-Up

1. Safety Results

The following analysis of long-term device safety was based on events from the implanted cohort of 910 patients that occurred after the randomization period and thus were not included in the safety results from the Original Follow-Up summarized above. This long term device safety and adverse event data are presented in Tables 7 to 9 below.

Thirty-four (34) system-complication events were observed during the post-randomization period of the study and are presented in Table 7 below. Twelve (12) of the device malfunctions listed below were due to IMD replacement due to battery depletion.

Table 7: System-Related Complication Rate – Extended Follow-Up

Complication	# of Events (%)
Infection	4 (0.44%)
Erosion	1 (0.11%)
Device Malfunctions	16 (1.76%)
Hematoma (requiring drainage)	3 (0.33%)
Lead Malfunction	2 (0.22%)
Pain	4 (0.44%)
Signal Capture Problem	4 (0.44%)

These 34 events were observed in 33 patients resulting in an overall complication rate of 3.63% from the post-randomization period of the study.

A total of 463 IMD replacement procedures were performed for patients in the Extended Follow-up of the ALERTS Clinical Study. Twelve (12) adverse events in 12 patients were observed during those procedures and are summarized in Table 8 below.

Table 8: Replacement Implant System-Related Complication Rate – Extended Follow-Up

Complication	# of Events (%)
Infection	1 (0.22%)
Erosion	1 (0.22%)
Device Malfunctions	6 (1.30%)
Pain	2 (0.43%)
Signal Capture Problem	2 (0.43%)
Total	2.59% (12/463)

A total of 703 explant procedures were performed for patients in the Extended Follow-up of the ALERTS Clinical Study. Four (4) adverse events were observed during those procedures and are summarized in Table 9 below.

Table 9: Explant Procedure System-Related Complication Rate – Extended Follow-Up

Complication	# of Events (%)
Hematoma (requiring drainage)	3 (0.43%)
Lead Malfunction	1 (0.14%)
Total	0.57% (4/703)

Adverse effects that occurred in the PMA clinical study (Original Follow-Up and Extended Follow-Up):

Sixty-five (65) system-related complication events were observed for the entire follow-up period of the ALERTS study are summarized in Table 10 below. Overall the acute procedural and long-term implantation risks of the device are comparable to a single chamber pacemaker.

Table 10: System-Related Complication Rate – Original and Extended Follow-Up

Complication	# of Events (%)
Cardiac perforation	2 (0.22%)
Device Malfunction	18 (1.98%)
Erosion	4 (0.44%)
Hematoma (requiring drainage)	3 (0.33%)
Infection	15 (1.65%)

Complication	# of Events (%)
Lead malfunction	3 (0.33%)
Lead migration/dislodgment	4 (0.44%)
Loss of sensing due to dislodgement or malfunction of lead	2 (0.22%)
Pain at or near the pocket site	9 (0.99%)
Signal capture problem	4 (0.44%)
Visible bump where implanted in the chest	1 (0.11%)

These 65 events were observed in 63 patients (out of 910 patient) resulting in an overall complication rate of 6.92% for the complete study follow-up.

2. Effectiveness Results

The analysis of effectiveness was based on ED visits from the 907 patients from the entire follow up period for the ALERTS Trial. Key effectiveness outcomes are presented in Tables 11 and 12 below.

Table 11 below shows the results from both components of the primary effectiveness endpoint of the Additional Analysis of ALERTS ED Visits. Based on study results, the null hypothesis was not rejected for PPV and was rejected for FPR. As a secondary endpoint the FPR for the ALARMS ON group was also tested for superiority with respect to ALARMS OFF group and test also demonstrated statistical significance with a p-value of <0.001.

Table 11: Primary Effectiveness Endpoint Results – Additional Analysis of ALERTS ED Visits

	ALARMS OFF – Symptoms Only	ALARMS ON – Alarm w/ or w/o Symptoms	P-Value
ED Visits	181	345	
True Positive	33	89	
False Positive	148	256	
PPV	18.23%	25.80%	0.0313*
FPR (FP/pt. year)	0.678 FP/pt. year	0.164 FP/pt. year	<0.001**

*One-sided Fisher's exact test for superiority (Significance level = 0.025)
**Generalized linear model based on a Poisson distribution and the canonical log link function.

These data can further be broken down into whether a patient with an alarm also experienced symptoms as shown in Table 12 below.

Table 12: Additional PPV Results – Additional Analysis of ALERTS ED Visits

	ALARMS OFF – Symptoms Only	ALARMS ON – Alarm and Symptoms	ALARMS ON – Alarm Only	ALARMS ON – Symptoms Only
ED Visits	181	135	210	625
True Positive	33	47	42	104
False Positive	148	88	168	521
PPV	18.23%	34.81%	20.00%	16.64%

Further analysis of the FP alarms revealed that a relatively small group of patients drove the FPR as shown in Table 13 below. Based on the data collected it was not possible to determine an adequate predictor for patients likely to experience multiple FP alarms.

Table 13: False Positive Frequency – Additional Analysis of ALERTS ED Visits

# of FP Alarms/Patient	# of Patients
0	744
1	106
2	37
3	9
4	8
5	2
6	0
7	1

Table 14 below presents the False Negatives (FNs) or missed ACS events that were recorded during the study period for the ALARMS ON group. A FN for either symptoms only or a Guardian System alarm could only be observed if the patient presented to the ED. If an ACS event or MI occurred and neither symptoms nor the guardian device prompted the patient to seek medical care it would not be captured in the following data.

Table 14: False Negatives – Additional Analysis of ALERTS ED Visits

	Alarm	Symptoms
FN - All ACS Events	104	42
FN - MIs	59 (3 STEMIs)	13 (1 STEMI)

The diagnostic performance of the device should be considered in clinical context and in comparison to the available alternatives.

For all ALERTS study patients, the presence of the device with ALARM ON increased the diagnostic accuracy (the PPV) compared to symptomatic patients without monitoring (ALARM OFF), (25.80% vs. 18.23%). Further, symptomatic patients with a positive alarm had a PPV that was higher than symptomatic patients with a negative alarm (34.81% vs. 16.64%).

Among patients without symptoms, those who presented to the ED had a 20.00% PPV. Without an alarm, these patients very likely would have gone undiagnosed.

The FPR (FP/patient year) was lower in the ALARMS ON group than in the ALARMS OFF group (0.164 vs. 0.678 FP/pt. year, P<0.001 for non-inferiority).

3. Subgroup Analyses

Analysis of subgroups for the Additional Analysis of ALERTS ED Visits did not reveal any significant conclusions.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 96 investigators of which none were full-time or part-time employees of the sponsor and one (1) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on March 16, 2016, the Circulatory System Devices Panel voted 8-4 that there is not reasonable assurance the device is safe, 12-0 that there is not reasonable assurance that the device is effective, and 12-0 that the

benefits of the device do not outweigh the risks in patients who meet the criteria specified in the proposed indication. The "Brief Summary of the Circulatory Ssytem Devices Panel Meeting – March 16, 2016" document can be accessed here: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM491425.pdf*

B. FDA's Post-Panel Action

After the Advisory Panel's review of the randomized portion/original follow-up data to support the Guardian System, FDA engaged with the applicant to develop the clinical analysis paradigm to include events from the Additional Analysis of ALERTS ED Visits that is described in Section X above. FDA has determined that the results of that analysis demonstrate a positive benefit-risk profile for the device.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The diagnostic performance of the device should be considered in clinical context and in comparison to the available alternatives. While the Advisory Panel voted that there was not a reasonable assurance of effectiveness, this re-analysis includes data that were collected outside the prespecified randomization period and thus were not reviewed under the original PMA or presented to the Advisory Committee.

For all ALERTS study patients, the presence of the device with ALARM ON increased the diagnostic accuracy (the PPV) compared to symptomatic patients without monitoring (ALARM OFF), (25.80% vs. 18.23%). Furthermore, symptomatic patients with a positive alarm had a PPV that was higher than symptomatic patients with a negative alarm (34.81% vs. 16.64%).

Among patients without symptoms, those who presented to the ED had a 20.00% PPV. Without an alarm, these patients very likely would have gone undiagnosed.

The FPR (FP/patient year) was lower in the ALARMS ON group than in the ALARMS OFF group (0.164 vs. 0.678 FP/pt. year, $P<0.001$ for non-inferiority).

The device improved the diagnostic accuracy (PPV) both for patients with and without symptoms, and the device did not increase the false positive rate (FPR) and may reduce it.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

In the randomized portion of the study, there were 31 system-related complication events in 30 subjects (3.30%) as defined for the primary safety endpoint. The primary safety endpoint of the trial was met with a posterior probability of >0.9999 which was above the significance threshold of 0.954. The primary safety endpoint was met.

In the Extended Follow-Up portion of the study, there were an additional 34 system-related complications in 33 subjects (3.63%).

These safety data represent data collected from 3450 implant years from the Original and Extended Follow-up.

The risks of the device have been well characterized and relate both to the procedural and device-related aspects as described above. Risks may also result from false positive or false negative results from the device.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the Additional Analysis of the ALERTS ED Visits conducted to support PMA approval as described above.

The data submitted in support of the PMA for the Angel Medical Guardian System demonstrates the following notable benefits:

a. Improved positive predictive value for ACS events in subjects presenting with symptoms
b. Improved positive predictive value for ACS events in subjects without symptoms
c. No increase, and a possible reduction in the false positive rate in subjects with device alarms ON compared to subjects with device alarms OFF.

While there is some uncertainty in assessing and quantifying these benefits, including the lack of statistical significance, the overall uncertainty regarding the benefits is acceptable.

Similarly, the risks of the device have been well characterized and relate both to the procedural and device-related aspects as described above. The risks also relate to the false positive and false negative device results. Overall, the uncertainty pertaining to the magnitude of these risks is low.

When considering the overall benefits and risks of the device, FDA concludes that the benefits outweigh the risks for the intended population. An important consideration is that the device fills an unmet medical need by providing more effective diagnosis of a life-threatening condition compared to relying on patient symptoms alone.

1. Patient Perspectives
   This submission contained some specific information on patient perspectives for this device; however, FDA did not find it useful in reaching its final decision.

In conclusion, given the available information above, the data support that for patients who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events. The probable benefits outweigh the probable risks. This is based on information from both the Original Follow-Up and the Extended Follow-up data sets from the ALERTS Clinical Study. The device fills an unmet medical need by providing more effective diagnosis of a life-threatening condition compared to relying on patient symptoms alone.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The AngelMed device improves diagnostic accuracy of ACS in a clinically meaningful portion of the intended use population, and the risks associated with use of the device are acceptable. The risks of the device were further mitigated with appropriate labeling.

XIII. CDRH DECISION

CDRH issued an approval order on April 9, 2018. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Study – AngelMed Guardian PAS. The Office of Surveillance and Biometrics will have the lead for studies initiated after device approval. Per protocol synopsis dated 03/29/18 the applicant agreed to conduct a post-approval study to assess diagnostic accuracy of the AngelMed Guardian System, and to evaluate the training programs for both physicians and patients.

The applicant will conduct a prospective, non-randomized, single arm, event-based, multicenter trial. The purpose of the study is to assess: (1) the diagnostic accuracy of the device, (2.1) the compliance of the prescribing physician, (2.2) the experience of the implanting physician, (2.3) the experience of the emergency department physician and (2.4) the patient compliance for “Emergency” and “See Doctor” alerts.

A total of 500 subjects who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events will be enrolled in the AngelMed Guardian PAS, for the purpose of accruing 314 True Positive or False Positive acute coronary syndrome (ACS) events.

The diagnostic accuracy primary endpoint is composed of the positive predictive value (PPV) and False Positive Rate (FPR) of the AngelMed Guardian System associated with acute coronary syndrome events. The PPV for Alarms (with or without symptoms) will be compared to a performance goal of 20%. The FPR (with or without symptoms) will be compared to a performance goal of 0.328 false positive events per patient year.

Secondary endpoints include: (1) the frequency of ALARM-Only ACS events (i.e., Silent ACS events), which is defined as the device alarm only presented to the emergency room (ER) physicians and not showing any other symptoms or discomfort/pain , and (2) the symptom-to-door times, defined as time between device alarm and medical presentation. Both secondary endpoints will be analyzed descriptively (frequency, mean, median and percentage of pre-hospital arrivals as a function of time).

Study subject visits will occur at implant, 7-14 days post-implant, 6 and 12 months post-implant and every 6 months thereafter until study exit or study completion. The PAS will be completed once 314 PPV events are collected.

In addition, the adequacy of the training program for the prescribing physician, implanting physician, emergency department physician, and patients will be assessed. Descriptive statistics (the raw count, percentage of all subjects, rate and number of sites) for the following assessments will be provided:

1. instances where the device was prescribed and implanted for patients that do not meet the proper labeling criteria to qualify for a Guardian implantable medical device (IMD)
2. instances of system revisions, e.g. any system problem that requires an invasive corrective procedure to resolve, required within 6 months of implant
3. instances of “Emergency” alarm non-compliance, failure to report to the ER within 72 hours of the alarm
4. instances of “See Doctor” noncompliance, defined as both failure to present to the doctor within 2 weeks of the alarm or reporting to the ER instead of to the doctor in response to the alarm
5. instances of patient non-success to reconfirm ability to recognize and distinguish between “Emergency” and “See Doctor”, defined by being able to report the proper actions to take for each and what to do when only symptoms occur in the absence of an alarm.
6. instances of percutaneous intervention (PCI) without at least one positive standard of care (SOC) test reported on a site-based and visit-based basis.

The applicant’s manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.