Rationale and design of the AngeLmed for Early Recognition and Treatment of STEMI trial: A randomized, prospective clinical investigation

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Significant improvements in door-to-balloon times have led to a reduction in mortality in ST-segment elevation myocardial infarction; however, mean symptom-to-door times remain at 2 to 3 hours. An intracardiac electrogram monitoring device may be beneficial in high-risk patients by alerting them to rapidly progressive ST-segment changes indicative of acute coronary occlusion. The Cardiosaver and DETECT phase I clinical studies demonstrated the safety, feasibility, and potential benefit of using an intracardiac electrogram monitoring device to alert the patient to seek medical attention. The goal of the randomized, prospective ALERTS Trial (Clinicaltrials.gov no. NCT00781118) is to evaluate the efficacy of an implantable monitoring device (IMD) in reducing the composite of either cardiac or unexplained death, new Q-wave myocardial infarction, or symptom-to-door time of >2 hours for confirmed thrombotic events. The IMD alerts the patient in real time when ST-segment deviation from a personalized baseline exceeds the trigger threshold. The trial is designed to enroll high-risk post-acute coronary syndrome patients or patients with previous multivessel coronary artery bypass surgery. All patients have the IMD implanted, with 1:1 unblinded randomization to the alerting feature being either turned on versus turned off for the first 6 months. Randomization occurs at the first follow-up visit, 7 to 14 days after the implantation of the IMD. Subjects then return for follow-up visits at months 1, 3, and 6 and thereafter every 6 months until closure of the investigational device exemption. Subjects who cannot be implanted successfully or who have the device explanted are removed from the study and followed up for a minimum of 30 days post-procedure. If a subject experiences a device-related complication and/or adverse experience, the subject is followed up until resolution or until the condition becomes stable and no further change is anticipated. (Am Heart J 2014;168:168-74.)

Early identification of ST-segment elevation myocardial infarction (STEMI) coupled with prompt treatment significantly improves clinical outcomes.[1-7] There has been a significant decline in mortality among STEMI patients over the last 30 years,[8,9] which is due at least in part to the more widespread use of primary percutaneous coronary intervention (PCI)[10] and improvements in adjunctive medical therapy but also due to decreased door-to-needle (DN) and door-to-balloon (DB) times.[11-13] Indeed, data from the National Registry of Myocardial Infarction demonstrated that a 30-minute reduction in DB time was associated with a 5.3% reduction in mortality, and a 30-minute reduction in DN time was associated with a 1% reduction in mortality.[13]

Regardless of whether restoration of flow is achieved through PCI or through fibrinolysis, rapid reperfusion is a key determinant of both short-term and long-term outcomes in STEMI.[6,7,14] Early initiation of treatment within the first 2 hours after coronary occlusion is critical to the prevention of irreversible myocardial damage, with most irreversible myocardial injury and fatal ventricular arrhythmias occurring within the first hour.[6,7,15-21] This is consistent with the well-supported hypothesis that "time is myocardium," and the corresponding notion that "time is outcome".[22] With respect to time to treatment, there is a 2-fold gradient in relative risk between the lowest risk category (<2 hours to treatment) and the highest risk category (>4 hours to treatment). This likely reflects the extent of necrosis that occurs before treatment initiation, with the greatest improvements in myocardial salvage occurring when the delivery of care occurs in the earliest stages of symptom onset.[23]

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Although DB and DN times have improved over the past 15 years, symptom-to-door times have proven difficult to improve and have remained relatively constant at approximately 2.7 hours.[22] For every 30-minute delay in treatment initiation, there is a 7.5% relative increase in 1-year mortality[7]; therefore, a reduction in symptom-to-door times may contribute significantly to a further improvement in mortality.[22] If plaque rupture(s) associated with transient occlusion can be identified, there may be the potential to completely abort STEMI and the associated myocardial necrosis. The lack of significant progress in symptom-to-door times may be due to a number of factors, including patient misconceptions of heart attack symptoms, silent myocardial infarctions (MIs), and misdiagnosis or failure to detect 12-lead electrocardiogram (ECG) changes consistent with infarction. Earlier detection of symptoms would translate to earlier treatment, simultaneously improving symptom-to-door times and perhaps even improving mortality.

Despite initiatives to educate patients about the importance of early recognition of symptoms, many patients continue to have misconceptions regarding the symptoms they should expect in the setting of a heart attack.[6,7,15-17,24] Focus groups conducted in the United States have demonstrated that patients expect symptoms of a heart attack to be pronounced and dramatic, causing pain in the chest so intense that it leads to collapse.[24] In reality, many patients feel no more than slight chest discomfort or pressure, and these symptoms are often mistaken as symptoms of indigestion. Atypical symptoms may not be recognized as signs of an MI, and even during the more classic symptoms of an MI, patient denial can prevent the patient from immediately calling emergency medical services.[22] Silent MIs may also hamper improvements in symptom-to-door time. Approximately 30% of MIs are silent or without typical chest symptoms.[25,26] After a silent MI, total mortality and cardiovascular mortality are significantly higher than for those who have not had a silent MI.[27]

Misdiagnosis or failure to detect an acute thrombotic occlusion can also be a factor, which prevents the implementation of timely treatment. There are limited sensitivity and specificity of the traditional 12-lead surface ECG in diagnosing STEMI in certain scenarios such as a posterior MI or a lateral wall (circumflex) MI. In these patients, the ECG often shows isolated anterior lead ST depression, which is misinterpreted as anterior myocardial ischemia rather than posterior MI.[28] Identification of acute thrombosis in a vessel supplying the posterior wall has proven to be a challenge, as its presentation on ECG is inconsistent, and the contribution of the posterior wall to the QRS complex in the anterior precordial leads is relatively small.[29] A study of 13,608 acute coronary syndrome (ACS) patients by Pride et al[28] showed that one-quarter of the 1,198 patients who presented with isolated anterior ST-segment depression were found to have an occluded culprit artery. Guidelines advocate that eligible patients undergo PCI within 90 minutes of arrival to the hospital; however, among patients in the study with an occluded artery (n = 314), the median time from ECG to PCI was 29.4 hours.[28] As demonstrated by the long median delay from ECG to PCI, very few patients with an anterior segment depression and an occluded culprit artery were recognized by physicians.

In addition to the increased risk of death, the morbidity associated with delays in seeking care, such as that associated with heart failure, leads not only to a reduced life expectancy but also to higher rates of hospitalization, the risk of sudden cardiac death, and a significant reduction in quality of life.[30]

In light of these limitations, an implanted device, which continuously monitors a patient's intracardiac electrogram may allow for the detection of ST deviation indicative of complete occlusion of the epicardial vessel within minutes of the occlusion and thereby improve "symptom-to-door" times. ST-segment changes often precede and may even occur in the absence of clinical symptoms in the setting of a heart attack. Two studies, the Cardiosaver study and the DETECT study, have demonstrated the safety and feasibility of an intracardiac electrogram monitoring (ICEM) device to alert patients to ischemic events associated with documented plaque rupture and thrombotic occlusion.[20] The ALERTS Trial, a phase II randomized clinical trial with up to 3,000 patients, aims to further evaluate the effectiveness of the Guardian System in the detection and alerting of rapidly progressive ST-segment shifts that could be indicative of coronary occlusion, irrespective of the presence of symptoms.

Study operations/organization

The trial is funded by Angel Medical Systems. The authors are responsible for the design and conduct of the trial, all trial analyses, drafting and editing the paper, and its final contents. The trial conduct is overseen by an executive committee that consists of members of the academic leadership of the trial and members from the sponsoring company. The executive committee provides oversight of trial conduct and data analysis, oversees publication of the trial results, and receives recommendations from the data safety monitoring board regarding possible additional analysis of modifications to the trial. The independent Clinical Events Adjudication Committee (CEAC) is composed of physicians who are external to both the sponsor and the trial and who possess the appropriate expertise to adjudicate events and to identify the relationship between trial events and the study device.

Study objectives

The primary objective of the ALERTS Trial is to evaluate the effectiveness of the AngelMed Guardian System as compared with the standard of care in reducing the

incidence of the composite of either cardiac or unexplained death, new Q-wave MI, or presentation >2 hours for a documented thrombotic coronary occlusion event among subjects at a high risk of recurrent MI.

Study design

This is an international phase II, randomized, prospective, clinical Food and Drug Administration investigational device exemption (IDE) pivotal investigation (Clinicaltrials.gov no. NCT00781118) of subjects who have been identified as being at high risk for MI based on having had ACS or previous bypass surgery. All subjects will be implanted with the Guardian System and will be randomized to treatment and control groups in a 1:1 allocation ratio, with the device being set to either alert or not alert patients, respectively.

The Guardian System for the ALERTS Trial will consist of a high-fidelity, implantable monitoring device (IMD) placed under the skin in the left pectoral region. The system will capture and store ECG data and detect shifts in ST-segment deviation relative to baseline ST-segment deviation data captured the preceding day. Patient-specific detection parameters for the IMD are created through the workstation (programmer), which looks for shifts in the ECG ST segment by comparing the real-time ST-segment voltage to a reference baseline ECG using a specific programmed detection algorithm. The Guardian System will then detect rapidly progressive ST-segment shifts greater than a preset threshold beyond the patient's own baseline ST range and alert the subject to seek medical attention through a vibratory alarm that is felt within the chest as well as a visual and auditory alarm that is transmitted to an external alarm device (EXD). These alarms are based on the international standard of medical equipment alarms.[31] When an alarm is initiated, the ECG data are saved by the IMD and can be retrieved for medical review.

Randomization will occur after the successful implantation of the device at the 7- to 14-day follow-up. Half of the subjects will be assigned to the treatment group using the Guardian System with an EXD with the alerting turned on; the other half of the subjects will be assigned to the control group with the alerting turned off and no EXD. Patients will not be blinded to their treatment group. Independent, blinded angiographic and ECG core laboratories are used to review angiograms to adjudicate whether a thrombotic occlusive event and a silent MI occurred, respectively and will be blinded to patient treatment group assignment. After randomization at day 7 to 14, all subjects will return for follow-up visits at 1, 3, and 6 months and every 6 months thereafter, until the IDE is closed. After the completion of the 6-month follow-up period, subjects in the control group will have the option to turn the Guardian System alerting feature on and to obtain an EXD. Subjects who are unable to be successfully implanted (due to device malfunctions, etc) or who have the device explanted are removed from the study and followed up for a minimum of 30 days postprocedure. Subjects who experience device-related complication and/or adverse events are followed up until resolution or until the condition becomes stable and no further change is anticipated. The anticipated time course of the study is approximately 7 years but may conclude sooner dependent on the declaration of early superiority in a bayesian analysis.

Primary end points

Safety. The primary safety objective is to demonstrate that ≥90% of subjects with the Guardian System implant do not experience system-related complications at the 6-month follow-up postprogramming visit. The primary safety objective will be analyzed when all randomized subjects have reached the 6-month follow-up visit. A *system-related complication* is defined as any adverse event related to a successfully implanted system that requires a system revision or invasive intervention, to resolve the complication. As such, infections resolved through the use of oral or intravenous antibiotics would not be considered as complications. The CEAC will determine the relationship, if any, between the adverse events and the Guardian System. The rates of false-positive ST-shift alarming and false-negative ST-shift alarming will be reported by sites and adjudicated by the CEAC, as will the association of symptoms with documented thrombotic occlusion. All adverse events will be stratified into 1 of 3 categories: serious, procedure related, and device related. Each stratum of adverse events will be summarized and reported across treatment groups as well as separately by treatment group.

Efficacy. The primary efficacy objective is to evaluate the effectiveness of the Guardian System in the detection of rapidly progressive ST-shift events indicative of coronary thrombosis. The primary efficacy end point is the composite of either (*a*) cardiac or unexplained death, (*b*) new Q-wave MI, or (*c*) time-to-door >2 hours for a documented thrombotic coronary occlusion event through 6 months of follow-up before crossover of patients who were previously not alarming. For this objective, the "time-to-door" for a thrombotic coronary occlusion event is measured from the time the device detects a rapidly progressive ST-shift event to time of arrival at a medical facility for a confirmed thrombotic coronary occlusion event.

Measurements and definitions. The CEAC will adjudicate all subject deaths. When available, medical examiner or autopsy reports will be used. When unavailable and if death was legally pronounced by a physician or prehospital provider, the subject medical records will be used. Finally, if no medical records are available, jurisdictional police reports and any other available

documentation will be reviewed. Subject death will be classified as cardiac, noncardiac, sudden cardiac, non-sudden cardiac, or unknown according to the following:

(i) Cardiac death: a death directly related to the electrical or mechanical dysfunction of the heart.
(ii) Noncardiac death: a death not classified as a cardiac death.
(iii) Unknown: if insufficient information is available to classify a death as cardiac or noncardiac, the death will be classified as unknown.

Confirmation of a true thrombotic coronary event will be determined by ECG data, elevated enzymes/biomarkers (creatine kinase [CK], CK-MB, or troponin), positive stress test, or angiographic presentation. A blinded, independent ECG core laboratory will review all ECGs collected at events and routine clinic visits for new Q waves using conventional criteria. Patients who arrive with a time-to-door time of >2 hours and who have no new Q-wave present will be diagnosed with a thrombotic coronary event if any of the following are present:

1. ST elevation, as determined through core laboratory assessment of a 12-lead ECG.
2. If the Guardian System detects a rapidly progressive ST-shift event, and a thrombotic coronary occlusion is not confirmed with a 12-lead ECG, thrombotic coronary occlusion event may be confirmed if any of the following are present:
   - Elevated enzymes/biomarkers (CK, CK-MB, or Troponin) per the standard of care at treating hospital, for example, above the upper limit of normal and considered within the "necrosis range" within 24 hours of the onset of ischemic discomfort.
   - Thrombotic occlusion on the angiogram as assessed by an independent angiographic core laboratory (the presence of thrombus, impaired epicardial flow or myocardial perfusion, or evidence of plaque rupture on angiography or intravascular ultrasound).

For patients with a Guardian System–detected event, new Q wave or death, available baseline and postevent 12-lead ECG data, and angiograms will be sent to the appropriate blinded core laboratories.

Secondary end points

Secondary end points include the individual components of the primary composite end point, as follows: (*a*) incidence of cardiac or unexplained death, (*b*) incidence of "new" Q-wave MI (by conventional criteria and confirmed via independent electrocardiogram [EKG] core laboratory), and (*c*) incidence of >2 hours until arrival at a medical facility after a confirmed thrombotic occlusive event. Additional secondary end points include (*d*) time from symptom recognition to arrival at a medical facility for a confirmed STEMI event (confirmed by ECG core laboratory); (*e*) time from Guardian System detection to presentation for ST-segment elevation MI (confirmed as STEMI by ECG core laboratory); (*f*) incidence of any MI (Q wave plus non–Q-wave MI), excluding non–Q-wave MI identified within 24 hours of an elective PCI (unless CK-MB >5 × Upper Limit of Normal [ULN]); (*g*) incidence of new plaque ruptures as determined by angiographic core laboratory (*new plaque rupture* is defined as new filling defect or hazy lesion on repeat coronary angiography that was not present at baseline angiography; (*h*) incidence of significant disease progression as determined by angiographic core laboratory (a patient is classified as having sustained significant disease progression on repeat coronary angiography if there is a change in the percent diameter stenosis of >20% compared with baseline angiography, subcategorized according to whether they required PCI).

Table I. Inclusion criteria

Subjects must meet all inclusion criteria to be enrolled in the study:

- Subject has ≥1 of the following conditions:
  1. Diabetes (type I or type II)
  2. Compromised renal function (Cr >1.2 mg/dL or creatinine clearance <50)
  3. TIMI risk score ≥3 using the appropriate UA/NSTEMI score or STEMI score matched to the syndrome
- Presents (within past 6 months) with a high-risk ACS (eg, unstable angina, STEMI, or NSTEMI) or has undergone or is scheduled for CABG within 6 months of implantation
- Has already undergone coronary angiography and revascularization, unless the physician determines it is appropriate to implant before or during the planned procedure
- Lives in a geographic area in close proximity (within 60 min by EMS) to any hospital that can treat AMI
- Subjects aged ≥21 years. Women of childbearing age must have a negative pregnancy test or confirmation of one of the following:
  1. Postmenopause or amenorrheic during the past year
  2. Surgical sterilization
  3. Use of effective contraceptive method

Abbreviations: *Cr*, creatinine; *UA/NSTEMI*, unstable angina/non–ST-elevation myocardial infarction; *NSTEMI*, non–ST-elevation myocardial infarction; *EMS*, emergency medical services; *AMI*, acute myocardial infarction.

Study population and patient selection

Subjects must be aged ≥21 years and present with high-risk ACS or multivessel coronary artery bypass surgery (CABG) as a result of coronary artery disease. Inclusion and exclusion criteria details are listed in Tables I and II. Patients who are unable to feel the vibration of the IMD when it is placed on the left pectoral side of their chest or cannot respond appropriately are deemed unsuitable candidates and will be excluded from the trial. All patients that meet eligibility criteria will be asked to participate in the study. Once a patient is deemed eligible for the trial, a member of the research team within the

Table II. Exclusion criteria

Potential subjects will be excluded from the study if any of the following apply:

- If the investigator does not think that the subject has the ability to respond appropriately to alarms (eg, illiteracy, poor memory or cognitive function, dementia, or other condition affecting memory function, etc).
- There is known compromised tissue at the site of lead implantation in the apex of the right ventricle (eg, prior infarct affecting the RV apex location).
- A permanent pacemaker or ICD is already in place, or the patient is indicated for ICD or pacemaker implantation based on the guidelines published by the American College of Cardiology as class I and IIa recommendations. Class IIb recommendations are at the investigator's discretion.
- Subject cannot feel the IMD vibration when placed on top of the skin on the left pectoral side of the chest.
- Subject has recurrent or persistent atrial fibrillation.
- Subject has recurrent or persistent nonsinus cardiac rhythm, second- or third-degree atrioventricular blocks, QRS duration >120 milliseconds, benign early repolarization, or Brugada syndrome.
- Subject has left ventricular hypertrophy evidenced by EKG criteria.
- Subject has any condition preventing the subcutaneous implantation of the Guardian System in a left pectoral pouch, such as superior vena cava thrombosis, subcutaneous tissue deemed inappropriate for the procedure or prior central venous access via portacath, Hickman, Groshong, or similar placed in a left pectoral location or left side PICC line.
- Subject has extremely heavy alcohol consumption (participates in binge drinking that leads to alcohol intoxication) or has history of alcohol or illicit drug abuse within past 5 years.
- There is evidence of unresolved infection (fever >38°C and/or leukocytosis >15000).
- Subject has history of bleeding disorders or severe coagulopathy (platelets <100000 plts/mL; aPTT or PT >1.3 × reference range).
- Subject has had a hemorrhagic stroke or transient ischemic attack in the past 6 months.
- Subject has other severe diseases, such as cancer or refractory congestive heart failure, associated with limitation of life expectancy (<1 year), which may lead to inadequate compliance to the protocol or confusing data interpretation.
- Subject has clinical conditions such as heart diseases, difficult-to-control blood pressure, difficult-to-control insulin-dependent diabetes or serious prior infections attributed to the diabetes, or others that, at the investigator's discretion, could seriously affect the subject's current clinical condition during study procedures.
- Subject has previous participation in the DETECT Study, current participation, or previous participation in another drug or device study in the past 30 days that conflicts with this study as determined by the study sponsor.
- Subject has experienced gastrointestinal hemorrhage in the past 6 months.
- Subject has any situation in which the use of aspirin is contraindicated for ≥6 months.
- Subject has epilepsy.
- Subject has known severe allergies (eg, peanut, bee sting, etc).

Abbreviations: *RV*, right ventricular; *ICD*, implantable cardioverter/defibrillator; *PICC*, peripherally inserted central catheter; *aPTT*, activated partial thromboplastin time; *PT*, prothrombin time.

hospital who is assigned to the ALERTS Trial will review the subject's profile to ensure that they meet the inclusion criteria, and that none of the exclusion criteria is met. A screening form is then completed, and the subject is an active study participant once the informed consent has been signed. Patients will then undergo a preprocedure evaluation that includes a complete medical history and physical examination, a 12-lead EKG, complete blood count, total cholesterol, high-density lipoprotein, an evaluation of the subject's ability to feel the IMD vibration at the surface, another review of the inclusion and exclusion criteria, and provision of written informed consent. Subjects who then continue to meet the selection criteria after completion of the preprocedure evaluation will be assigned an enrollment number.

Randomization and treatment protocol

Patients are randomized 1:1 to the treatment and control groups with implantation of the Guardian System IMD with alerting turned "on" or with the Guardian System IMD alerting turned "off," respectively. The randomization is stratified by site with a blocking scheme that consists of blocks of randomly varying size and occurs after successful implantation of the Guardian System device at the 7- to 14-day follow-up visit before programming.

An IS-1 pacemaker lead is required for attachment to the Guardian System and subsequent implantation. The lead will be threaded through the tricuspid valve into the right ventricle and placed in the apex of the right ventricle, where it will attach itself to the endocardium. Standard postprocedure follow-up will be performed according to the institution's procedures. Before discharge, data will be retrieved from the IMD to check for proper performance and to optimize the device for baseline electrogram analysis. In addition, a postoperative chest x-ray and standard 12-lead ECG will also be obtained. Any adverse events and complications will be recorded. Medications will also be recorded at this time.

At the 7- to 14-day postimplant follow-up, the patient will undergo either a standard or nuclear stress test (at the discretion of each investigator) and will be randomized to the control arm or treatment arm of the trial. At this visit, the patient will undergo an examination to record any anginal equivalents, and a 12-lead surface ECG will be performed. Medications will again be recorded at this time, as starting or stopping certain drugs can cause a chronic change in ST levels, and programming will not occur until 7 days, after the changes are implemented. This programming update will establish the alerting threshold across the range of ST elevation–heart rate changes of each individual patient. At this time, the Guardian IMD will also be interrogated to ensure that the device is functioning as necessary and that the electrogram monitoring parameters are adequate. If stress testing is done, the IMD will be interrogated after the stress testing procedure to adjust the device programming, so that rate-related ischemia does not trigger the alarm. Subjects who are randomized to the treatment group will have IMD alerting turned on with an EXD in place, which transmits the vibratory, visual, and audible alarms and will be trained on the use of the Guardian System and how to respond to alarms. Subjects randomized to the control group will receive the standard

of care, per the treating physician. Both groups will be educated regarding the importance of seeking immediate medical attention should signs or symptoms of an ischemic event occur. With the exception of the alarm of the IMD being turned off and having no EXD in place, the IMD will be programmed in the same way in the control group as in the treatment group.

All patients will have follow-up visits at 1, 3, and 6 months, then every 6 months from that point onward, to review the patient's IMD event status, to obtain updated records of medications taken and to reinforce training on responding to alarms and/or symptoms. For the control arm subjects, reprogramming will occur at the initial 6-month visit to have the IMD alerting turned on, consistent with the parameters of the treatment arm. At this time, control subjects will also be trained to identify and respond to alarms. At each subject visit, a 12-lead ECG will be obtained, data will be retrieved from the IMD to make monitoring parameter changes as necessary, and any adverse experiences or complications will be recorded. For the first 6 months of follow-up, the patients and site staff in the control group will be blinded to the stored ECG data transmitted to the programmer to avoid potentially biased treatment changes. In the event of an emergency alarm, patients should have the time of symptom onset recorded, and if no symptoms were present, the time will be recorded as null. The subjects must also undergo a cardiac evaluation consistent with the standard of care, which includes serial cardiac enzymes, serial ECGs, recording of adverse events, medications, and if necessary, a nuclear stress test, a positron emission tomography scan, or angiography.

Statistical considerations

The sample size for this study is not predetermined but is based upon a bayesian adaptive sample size determination. The bayesian adaptive design is used so that the appropriate sample size can be evaluated at different time points during the trial. To determine whether to stop or to continue subject accrual, several planned analyses will occur. The first planned analysis will occur once 600 subjects have been enrolled and randomized, with subsequent analyses occurring at every 300 randomizations. The interim analyses are termed *sample size looks*; during each analysis, the decision to stop or continue subject accrual will be based on the predictive probability of eventual success for the primary efficacy objective.

If the initial interim analysis (n = 600) results in a decision to stop accrual, a single analysis to determine efficacy and safety will be conducted once all randomized subjects have reached the 6-month follow-up visit. If accrual is stopped at a larger sample size (n $\geq$900), there will be an interim analysis to detect "early superiority," in addition to the final analysis. The "early superiority" analysis will occur at either (1) the time when it was decided to stop accrual; (2) the time when n/2 subjects have completed 6 months of follow-up; or (3) the time, where $\geq$10 events are known to have occurred, whichever occurs latest. If "early superiority" is declared for the primary efficacy objective results, the primary safety objective and all secondary objectives will be evaluated at the same time. If "early superiority" is not declared, another, final analysis of the primary efficacy, safety, and secondary objectives will occur when all randomized subjects have completed the 6-month follow-up.

The predicted event rate, in the control group, of reinfarction and sudden death after the index event is 4.8% for STEMI and 5.6% for non–ST-elevation MI/unstable angina. Prior research suggests that most of these events will occur within 6 months of the index event.[32] However, there is still uncertainty in the rate of events to expect in the control population because the rate of new Q-wave MI was not recorded. With the changes in the definition of MI moving toward detection of necrosis, the recent literature does not report Q-wave MI event rates. In addition, there is uncertainty in the size of the treatment effect (ie, the reduction in rate of events that can be achieved in the treatment group). To account for this uncertainty, a bayesian adaptive design is used so that sample size can be dynamically determined during the course of the trial.

Conclusion

The ALERTS Trial will enroll subjects who are at high risk for an MI based on ACS or history of a multivessel CABG procedure. The trial incorporates the use of an ICEM device implanted into the left pectoral region of the subject, which alerts the patient to seek medical attention when significant ST-segment changes indicate an acute thrombotic event or plaque rupture. Two phase I clinical trials, the Cardiosaver and DETECT studies, have also studied the use of an ICEM device and represent 58.2 patient years of monitoring and >18 million monitored ECG segments collectively in a population at high risk for thrombotic events.[33] These studies demonstrated the feasibility and potential effectiveness of an ICEM device and did not introduce any new safety risks when compared with the implantation of a single-chamber pacemaker. The results support the expansion of the IDE feasibility study to a phase II randomized, prospective, clinical trial in the form of the pivotal ALERTS Trial. This trial aims to investigate the effectiveness of an ICEM Guardian System to alert high-risk patients to seek immediate medical attention in the setting of ST-segment changes signifying coronary occlusion and possible impending MI. The efficacy of the trial will be measured by a reduction in the composite end point of either cardiac or unexplained death, new Q-wave MI, or >2 hours to reach the hospital in the presence of a confirmed occlusive coronary event.

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