AngelMed Guardian System

P150009

LTJG Stephen Browning
U.S. Public Health Service
Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

March 16, 2016
FDA Presentations

• Introduction – LTJG Stephen Browning
• Statistical Presentation – Dr. Zhiheng Xu, PhD
• Clinical Presentation – Dr. Kimberly Selzman, MD
• Conclusion – LTJG Stephen Browning
Physical Device Description

Guardian System Device Components
- Implantable Medical Device (IMD)
- External Device (EXD)
- Programmer
ST-Shift Measurement

- Collect electrograms (tip-can) every 90 seconds (30 seconds if previous electrogram was abnormal)
- Compare ST Deviation (ST and PQ segment difference) to a 24 baseline
- Six “shifted” beats → shifted electrogram
- Three consecutive shifted electrograms → possible ischemia and alarm
- Heart rate tracking (w/no alarm at high heart rates)
Physical Device Description

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- External Device (EXD)
- Programmer
Physical Device Description

Guardian System Device Components
- Implantable Medical Device (IMD)
- External Device (EXD)
- Programmer
Proposed Indications for Use

The Guardian System is indicated to alert patients with prior acute coronary syndrome events to ST segment changes indicating acute coronary occlusion.

Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.
Non-Clinical Testing

- Biocompatibility
- Sterility & Packaging
- Electrical Safety and EMC
- Human Factors risk assessment

- Software Validation and Documentation
- Mechanical and Electrical Device Integrity
- *In vivo* animal studies

Non-Clinical Testing is complete.
FDA Presentations

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P150009 AngelMed Guardian System

Statistical Presentation

Zhiheng Xu, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics
FDA/CDRH
Outline

• ALERTS Clinical Trial Design
• Interim Analyses
• Primary Safety Endpoint
• Primary Effectiveness Composite Endpoint
  – Time-to-door >2 hours component
  – Death component
  – New Q-wave MI component
• Positive Predictive Value (PPV)
• Conclusion
ALERTS Clinical Trial

Pre-procedure Evaluation

<table>
<thead>
<tr>
<th>Enrollment (N=1020)</th>
<th>Implant (N=910) Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not implanted (N=110) #</td>
<td>Δ - 3 not randomized due to 2 discontinued and 1 death</td>
</tr>
</tbody>
</table>

Device Implant

<table>
<thead>
<tr>
<th>ALERTS On (Treatment) (N=451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALERTS Off (Control) (N=456)</td>
</tr>
</tbody>
</table>

Randomization (N=907)

Follow-Up

<table>
<thead>
<tr>
<th>1, 3, 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 3, 6 months*</td>
</tr>
</tbody>
</table>

* - Alerts were turned on after six-month follow-up.

End of ALERTS Study Post 6-month evaluation

# - Change mind (51), developed exclusion (35); unable to implant (8), other (15), death (1)
Study Population

• The ALERTS Clinical Study subject profile involved the following requirements:
  – Advanced Multi-vessel Coronary Disease
  – An index ACS event (MI, Unstable Angina or CABG) within six months of subject enrollment
  – Additional risk factors/co-morbidities (diabetes, TIMI risk score >3, or renal insufficiency)
Prospective Bayesian Adaptive Design

Planned Interim Analysis

1\textsuperscript{st} Interim Look

N=600

2\textsuperscript{nd} Interim Look

N=900

3\textsuperscript{rd} Interim Look

N=1,200

Intermediate looks at subsequent every 300 subjects

Maximum

N=3,000

- Stop Enrollment if
  - $P_n > S_n$ (success bound) or
  - $P_n < F_n$ (futility bound)
- Otherwise, enroll another 300 subjects.
- $P_n = \Pr[R_t < R_c \mid \text{interim data}]$
Performed Interim Analyses

Sponsor stopped the trial at n=1020

1020 is the maximum number FDA had agreed on in order to continue enrollment during the interim look at 900 subjects. However, FDA had not agreed on stopping the trial at 1020 subjects.

1st Interim Look

- N=600
- N=900
- N=1,200
- Maximum N=3,000

2nd Interim Look

- **Assumption issue**
  - New Q-waves come and go (contradictory to the stable Q wave assumption)

- **Data quality issues**
  - Incomplete or inaccurate data entry
  - Reporting delay

- **Sponsor’s decision:** stop the trial at n=1020 even though interim analysis at N=600 and 900 have indicated that enrollment should continue
Study Conduct Issue

• Sponsor’s decision of enrollment termination is viewed by FDA as a significant **protocol violation**
  – Loss of power (the ability to claim the truly treatment success)
  – The operating characteristic of the trial is not the same as planned
  – The validity of the trial may be undermined from a compliance, data quality and trial integrity perspective
  – The Bayesian analyses on the primary and secondary endpoints may be compromised.
  – Although FDA agreed to expand enrollment to 1020 subjects in order to cover the planned interim look at N=900, FDA did not agree to stopping the trial early. The interim looks showed that the trial should continue.
Panel Question:

The panel will be asked to comment on study conduct issue of early termination of ALERTS clinical trial.
Primary Safety Endpoint

• **Goal:** >90% implanted subjects free of system-related complications at six months
  – System-related complication refers to any adverse event related to a successfully implanted system that requires a system revision (invasive intervention) to resolve.

• **Success Criteria:** \( Pr(p>0.9| \text{data}) > 0.954 \)
  – A high posterior probability in a Bayesian framework is analogous to a small p-value (e.g. \( p<0.05 \)) in a Frequentist framework.
  – 0.954 was determined by trial and error in the simulation to achieve a type I error rate that is at most 0.05.
Primary Safety Endpoint Results

<table>
<thead>
<tr>
<th>All Subjects with Successful Implant (N = 910)</th>
<th>Primary Safety Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free subjects</td>
<td>866</td>
</tr>
<tr>
<td>Subjects with events</td>
<td>30</td>
</tr>
<tr>
<td>% Event Free</td>
<td>96.7% (866/896)</td>
</tr>
<tr>
<td>Posterior Probability $Pr(p&gt;0.90</td>
<td>data)$</td>
</tr>
</tbody>
</table>

1: 14 unobserved (no event but insufficient follow-up)
2: 30 subjects had 31 system-related complications
3: Significance threshold: 0.954

Conclusion: Primary safety endpoint was met based on pre-specified protocol.

Caution should be given when interpreting safety data as study conduct issue of trial early termination.
Primary Effectiveness Endpoint

• Composite Endpoint
  – Cardiac or unexplained death, or
  – New Q-wave MIs, or
  – Time-to-door > 2 hours after detected thrombotic event

• Event Rate: $R_t$ for treatment and $R_c$ for control
  – Proportion of subjects who experience the event in 6 months
  – Patient-level analysis per protocol

• Success Criteria: $\pi = \Pr(R_t < R_c | data) > 0.983$

  1. A high posterior probability in a Bayesian framework is analogous to a small p-value (e.g. $p<0.05$) in a Frequentist framework.
  2. 0.983 was determined by trial and error in the simulation to achieve the overall type I error of the design not exceed 0.025.
Bayesian Model

\[ R_t \sim \text{Beta}(1,1), \]
\[ R_c \sim \text{Beta}(1,1) \]

Posteriors
\[ R_t \sim \text{Beta}(1+E_t,1+NE_t), \]
\[ R_c \sim \text{Beta}(1+E_c,1+NE_c) \]

Success if \( \pi > 0.983 \)

Posterior Probability of Event Reduction
\[ \pi = \Pr(R_t < R_c | \text{data}) \]

\( R_t \): treatment event rate
\( R_c \): control event rate
Primary Effectiveness Endpoint

- Composite endpoint: patients with any one of three components
- Will discuss each component individually
Time-to-door > 2 Hours Component

- Time-to-door: Time between ST shift detection and presentation for confirmation
- Confirmed positive event for ischemia by AGEA (either ST elevation on ECG, positive biomarkers, a positive stress test, or a positive angiogram)

179 ST detections in Treatment (n=95)
- 34 Confirmed Positive by AGEA (n=27)

181 ST detections in Control (n=96)
- 18 Confirmed Positive by AGEA (n=17)

n - number of subjects.
AGEA - ALERTS Group for Endpoint Adjudication (AGEA) Committee
Question: What is the maximum allowable time for the time-to-door >2 hr events in the primary effectiveness endpoint?
Look-back Window

- Maximum allowable time between ST shift detection and the “late arrival” for a confirmed occlusive event
  - ST shift detection #1: time-to-door=25 days
  - ST shift detection #2: time-to-door=5 days
  - 7-day look-back window: one time-to-door>2hrs event (ST shift detection #2)
  - 30-day look-back window: two time-to-door>2hrs events (ST shift detection #1 and #2)
Time-to-door > 2 Hours

<table>
<thead>
<tr>
<th>Look-back Window</th>
<th>Control (N=456)* n (%)</th>
<th>Treatment (N=451)* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Day</td>
<td>8 (1.8%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>10-Day</td>
<td>9 (2.0%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>30-Day</td>
<td>13 (2.9%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>50-Day</td>
<td>15 (3.4%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>70-Day</td>
<td>16 (3.6%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>90-Day</td>
<td>17 (3.8%)</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>

* - Number of missing subjects in control (n=10) and treatment (n=12) for this component.
Statistical Analysis Issue

- Multiple look-back windows
  - No multiplicity adjustment was planned or conducted
    - The more hypothesis testing in a data set, the higher likelihood of getting significant result(s).
  - Neglecting multiplicity could lead to false declaration of significance and therefore spurious inference
The panel will be asked to comment on statistical analysis issue of multiple look-back windows.
## Death and New Q-wave MI Components

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=456)</td>
<td>(N=451)</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac or Unexplained Death</strong></td>
<td>1 (0.2%)</td>
<td>3* (0.7%)</td>
</tr>
<tr>
<td><strong>New Q-Wave MI</strong></td>
<td>14** (3.3%)</td>
<td>10 (2.4%)</td>
</tr>
</tbody>
</table>

* - One treatment subject (042-005) had both death and time-to-door>2 hrs events.
** - Three control subjects (017-011, 062-019, 067-001) had both new Q wave MI and time-to-door >2 hrs events.
Δ - Number of missing subjects in control (n=9) and treatment (n=10) for death component.
# - Number of missing subjects in control (n=29) and treatment (n=31) for new Q-wave component.
Primary Effectiveness Endpoint

<table>
<thead>
<tr>
<th>Look-back Window</th>
<th>Control (N=456)# n (%)</th>
<th>Treatment (N=451)# n (%)</th>
<th>95% BCI (ON-OFF)</th>
<th>Posterior Prob. $\pi = P_r(R_{ON} &lt; R_{OFF} \mid \text{data})^*$</th>
<th>Trial Success ($\pi &gt; 0.983$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Day</td>
<td>21 (4.9%)</td>
<td>16 (3.8%)</td>
<td>(-3.93%, 1.67%)</td>
<td>0.7856</td>
<td>No</td>
</tr>
<tr>
<td>10-Day</td>
<td>22 (5.1%)</td>
<td>16 (3.8%)</td>
<td>(-4.22%, 1.48%)</td>
<td>0.8279</td>
<td>No</td>
</tr>
<tr>
<td>30-Day</td>
<td>25 (5.8%)</td>
<td>16 (3.8%)</td>
<td>(-5.02%, 0.84%)</td>
<td>0.9177</td>
<td>No</td>
</tr>
<tr>
<td>50-Day</td>
<td>27 (6.3%)</td>
<td>16 (3.8%)</td>
<td>(-5.55%, 0.43%)</td>
<td>0.9527</td>
<td>No</td>
</tr>
<tr>
<td>70-Day</td>
<td>28 (6.5%)</td>
<td>16 (3.8%)</td>
<td>(-5.82%, 0.24%)</td>
<td>0.9644</td>
<td>No</td>
</tr>
<tr>
<td>90-Day</td>
<td>29 (6.8%)</td>
<td>16 (3.8%)</td>
<td>(-6.06%, 0.03%)</td>
<td>0.9740</td>
<td>No</td>
</tr>
</tbody>
</table>

* - The significance threshold for the posterior probabilities of event reduction is 0.983. The analysis is for completers only.
# - Number of missing subjects in control (n=28) and treatment (n=28) for the composite endpoint.

Conclusion: Primary effectiveness endpoint was not met.
$R_t$: treatment event rate
$R_c$: control event rate
New Q-wave MI: Single Baseline

• Single baseline: randomization ECG
  – pre-specified in SAP

<table>
<thead>
<tr>
<th>Baseline at Randomization</th>
<th>1 Month Visit</th>
<th>3 Month Visit</th>
<th>6 Month Visit</th>
<th>New Q-wave MI (single)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X</td>
<td>Yes</td>
</tr>
</tbody>
</table>

X : present. – : absent
“Dual-baseline” Post-hoc Analysis

- Reliability issue at ECG baseline at randomization data
- Dual baseline: pre-implant ECG and randomization ECG
  - Proposed after the sponsor was unblinded but core lab who read all ECG was still blinded.

<table>
<thead>
<tr>
<th>Baseline Pre-Implant</th>
<th>Baseline at Randomization</th>
<th>1 Month Visit</th>
<th>3 Month Visit</th>
<th>6 Month Visit</th>
<th>New Q-wave MI (single)</th>
<th>New Q-wave MI (dual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>–</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>X</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

X: present. –: absent
# New Q Wave MI

<table>
<thead>
<tr>
<th>Baseline Used</th>
<th>Control (N=456)*</th>
<th>Treatment (N=451)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Single – At Randomization</strong></td>
<td>14 (3.3%)</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td><strong>Dual – Pre-Implant and At Randomization</strong></td>
<td>13 (3.0%)</td>
<td>7 (1.7%)</td>
</tr>
</tbody>
</table>

* - Number of missing subjects in control (n=29) and treatment (31) for new Q-wave MI.
Conclusion: “Dual-baseline” post-hoc analysis shows the primary effectiveness endpoint was met* with look-back windows of at least 70 days.

Note: Post-hoc analysis results should be interpreted with caution due to the nature of post-hoc.

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### Look-back Window Post-hoc Analysis

| Look-back Window | Control (N=456)# n (%) | Treatment (N=451)# n (%) | 95% BCI (ON-OFF) | Posterior Prob. \( \pi=Pr(R_{ON} < R_{OFF} | data) \)* | Trial Success* (\( \pi>0.983 \)) |
|------------------|------------------------|--------------------------|------------------|---------------------------------|---------------------------|
| 7-Day            | 20 (4.7%)              | 13 (3.1%)                | (-4.28%, 1.02%)  | 0.8833                          | No                       |
| 10-Day           | 21 (4.9%)              | 13 (3.1%)                | (-4.56%, 0.84%)  | 0.9110                          | No                       |
| 30-Day           | 24 (5.6%)              | 13 (3.1%)                | (-5.36%, 0.23%)  | 0.9637                          | No                       |
| 50-Day           | 26 (6.1%)              | 13 (3.1%)                | (-5.89%, -0.18%) | 0.9812                          | No                       |
| 70-Day           | 27 (6.3%)              | 13 (3.1%)                | (-6.16%, -0.38%) | 0.9870                          | Yes                      |
| 90-Day           | 28 (6.5%)              | 13 (3.1%)                | (-6.43%, -0.60%) | 0.9908                          | Yes                      |

* - The significance threshold for the posterior probabilities of event reduction is 0.983. This analysis is for completers only.

# - Number of missing subjects in control (n=28) and treatment (n=28) for the composite endpoint.
Note: post-hoc analysis results should be interpreted with caution due to the nature of post-hoc.

\( R_t \): treatment event rate
\( R_c \): control event rate
Post-hoc Analysis Issue

“Dual baseline” post-hoc analysis

- “Dual baseline” was proposed after data was unblinded and the risk of bias is high.
- Event reduction could be artificially increased due to the use of “dual baseline”.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Composite Endpoint</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_c$</td>
<td>$R_t$</td>
<td>$R_t - R_c$</td>
</tr>
<tr>
<td>Single</td>
<td>3.8%</td>
<td>0.9%</td>
<td>-2.9%</td>
</tr>
<tr>
<td>Dual</td>
<td>6.5%</td>
<td>3.1%</td>
<td>-3.4%</td>
</tr>
</tbody>
</table>

$R_c$: control event rate  $R_t$: treatment event rate
Panel Question:

The panel will be asked to comment on post-hoc analysis issue of using dual-baseline.
Time-to-door: key secondary endpoint

- Binary outcome: time-to-door > 2 hours or not
  - Treatment event rate: 4 (0.9%)
- Continuous outcome: mean time-to-door
  - Treatment mean time 2.66 hrs (SD=5.3 hrs)

<table>
<thead>
<tr>
<th>Look-back Window</th>
<th>Reduction in Events (time-to-door&gt;2hrs)</th>
<th>Reduction in Time (mean time-to-door)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Time-to-door &gt; 2 hrs (%)</td>
<td>Control Mean time-to-door (SD)</td>
</tr>
<tr>
<td></td>
<td>Posterior Prob.</td>
<td>Success</td>
</tr>
<tr>
<td>7-Day</td>
<td>8 (1.8%)</td>
<td>0.8614</td>
</tr>
<tr>
<td>30-Day</td>
<td>13 (2.9%)</td>
<td>0.9840</td>
</tr>
<tr>
<td>90-Day</td>
<td>17 (3.8%)</td>
<td>0.9978</td>
</tr>
</tbody>
</table>

Conclusion: The results for time-to-door secondary end point is significant (>0.975) based on pre-specified study protocol. However, if this endpoint becomes the primary endpoint as the sponsor proposed in the IFU, then the significant threshold can’t be determined post-hoc. Therefore the interpretation of this results should be taken with caution.
Device Diagnostic Performance

- Sensitivity, specificity, and negative predictive value (NPV) cannot be accurately calculated
  - Sensitivity = TP/ (TP+FN)
  - Specificity = TN/(FP+TN)
  - NPV = TN/(TN+FN)

<table>
<thead>
<tr>
<th>Device Alarm</th>
<th>True disease condition (ACS event)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>True Positive (TP)</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negative (FN)</td>
</tr>
</tbody>
</table>

False negatives (FN) and true negatives (TN) cannot be accurately determined for Control patients or Treatment patients who do not present due to an alarm
Positive Predictive Value (PPV)

- Alerts off for Control subjects
- PPV for alarms in treatment only (n=179)
  - True Positive (TP): CPA (Confirmed Positive Alarms)
  - False Positive (FP): NCPA (Non-confirmed Positive Alarms)
  - PPV = CPA/(CPA+NCPA)
Treatment Alarms (N = 179)

Excluded Alarms (N=72)

Aggregated Alarms (N = 15)

Remaining Alarms (N=92)

Non-confirmed Positive Event Alarms (NCPA) (N = 22+10=32)

Confirmed Positive Event Alarm (CPA) (N = 60)

31 AGEA adjudicated events +
29 sponsor adjudicated events

Inpatient (N = 18)
Noncompliant (N = 19)
Programming Errors (N = 17)
Incomplete (N = 8)
Medical Procedure Induced (N = 9)
Algorithm Anomaly (N = 1)

Treated as CPA in Sponsor’s Calculation (N = 10)
Sleep apnea n=1
Vasospasm =5
Bundle branch n=4
## Positive Predictive Value (PPV)

<table>
<thead>
<tr>
<th>Method</th>
<th>PPV Point Estimate*</th>
<th>PPV 95% CI**</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-Recommended Method</td>
<td>65.2% (60/92)</td>
<td>(54.2%, 74.9%)</td>
</tr>
<tr>
<td>Sponsor’s Method</td>
<td>76.1% (70/92)</td>
<td>(67.0%, 85.2%)</td>
</tr>
</tbody>
</table>

* - Estimate Based on raw Counts  
** - Estimate from GEE model to account for within patient correlation

Caution should be given when interpreting this result since more than 40% treatment alarms have been excluded from PPV analysis.
Panel Question:

The panel will be asked to comment on the concern when interpreting device diagnostic performance that 40% of alarms were excluded from the PPV analysis.
Statistical Conclusion

• The primary safety endpoint was met.
• The primary effectiveness endpoint was not met.
• Multiple study conduct issues result in difficulties in interpreting clinical data and analysis:
  – The sponsor’s decision of enrollment termination is a significant protocol violation.
  – Multiplicity is not adjusted for multiple look-back windows on primary effectiveness endpoint.
  – The use of dual baseline could introduce potential bias and overestimate treatment effects.
  – Caution should be given to the PPV result since more than 40% treatment alarms have been excluded from PPV analysis.
FDA Presentations

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- Statistical Presentation – Dr. Zhiheng Xu, PhD
- Clinical Presentation – Dr. Kimberly Selzman, MD
- Conclusion – LTJG Stephen Browning
Angel Medical Guardian Device
ALERTS Trial
Clinical Review

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Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration
March 16, 2016
FDA’s Clinical Review: ALERTS Trial

1. Safety Results
2. Effectiveness Results
   a) New Q wave MI
   b) Time to Door > 2 hours
3. Positive Predictive Value
4. Proposed IFU
5. Post Approval Study
The ALERTS Trial

• Prospective Bayesian RCT

• All subjects were implanted with the Guardian device

• Randomized to:
  – Alarm ON (treatment)
  – Alarm OFF (control)

• Primary endpoint:
  – Reduction in cardiac death,
  – New Q wave MI,
  – Delayed patient presentation for ACS
The Guardian Device

- Similar to a VVI pacemaker
- Continuously monitoring the intracardiac electrogram (EGM)
- Assessing changes in ST segment as an intracardiac ischemia monitor
Electrogram (EGM) vs ECG

- EGM ST changes traditionally for arrhythmia and rate detection
- EGM ST changes for ischemia detection is relatively new
- 2 prior ambulatory EGM studies (n=37)

Initial Clinical Results Using Intracardiac Electrogram Monitoring to Detect and Alert Patients During Coronary Plaque Rupture and Ischemia. Fischell et al. JACC 2010.
# ALERTS Results: Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (Off)</th>
<th>Treatment (On)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Female sex</td>
<td>34%</td>
<td>30%</td>
</tr>
<tr>
<td>Caucasian race/ethnicity</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>Prior STEMI, NSTEMI</td>
<td>25% 28%</td>
<td>24% 28%</td>
</tr>
<tr>
<td>Prior unstable angina</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>History of silent MI</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>LVEF</td>
<td>54%</td>
<td>54%</td>
</tr>
<tr>
<td>Diabetes, RI, TIMI&gt;3</td>
<td>49%, 16%, 3.6</td>
<td>46%, 18%, 3.7</td>
</tr>
<tr>
<td>History of smoking</td>
<td>69%</td>
<td>71%</td>
</tr>
<tr>
<td>BMI</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>
Safety Results

Goal: >90% system-related complication free rate (CFR)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Event s (n)</th>
<th>% of cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>11</td>
<td>1.2%</td>
</tr>
<tr>
<td>Battery failures</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pocket pain, erosion, protruding device</td>
<td>9</td>
<td>0.9%</td>
</tr>
<tr>
<td>Lead dislodgement, migration, malfunction</td>
<td>6</td>
<td>0.6%</td>
</tr>
<tr>
<td>Perforation</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Lead adaptor replacement</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>31</strong></td>
<td><strong>3.3%</strong></td>
</tr>
</tbody>
</table>

Comp. Free Rate = 96.7%; posterior probability > 0.9999
Primary Effectiveness Endpoint:

1. Cardiac/Unexplained death
2. Time to door > 2 hours (using 90 day window)
3. New Q wave MI

Treatment (N=451) → N = 439

- Composite primary endpoint (n=16)

Control (N=456) → N = 446

- Composite primary endpoint (n=29)

Posterior Probability is 0.974 (<0.983)
Primary Effectiveness Endpoint: Cardiac or Unexplained Death

- 6 deaths total;
  - 4 were cardiac/unexplained;
    - Treatment Group: 3 deaths (0.7%)
    - Control Group: 1 death (0.2%)
Primary Effectiveness Endpoint: New Q wave MI

- New Q wave on ECG at 6 months
- New Q wave needs to be in an anatomic region with no prior Q wave
- Differs from Universal Definition of MI*
- Single Q waves may not represent a prior MI
  - Lead placement
  - Electrolyte imbalance

*Thygesen K, et al. ESC/ACCF/AHA/WTF Task Force for the Universal Definition of MI JACC 2012
Primary Effectiveness Endpoint: New Q wave MI

Serial over-read of ECGs to ensure Q waves persisted

<table>
<thead>
<tr>
<th>Randomization</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
Primary Effectiveness Endpoint:
New Q wave MI: Dual Baseline

<table>
<thead>
<tr>
<th>Pre-implant</th>
<th>Randomization</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

7 new QWMIs developed the Q wave at 6 mo
Primary Effectiveness Endpoint: new Q wave MI: dual baseline

**Single baseline**
- New Q wave MI
  - Treatment n=10 (3.3%)
  - Control n=14 (2.4%)

**Dual baseline**
- New Q wave MI
  - Treatment n=7 (1.7%)
  - Control n=13 (3.0%)

Combined Primary Effectiveness Endpoint (90 day)
- Single: Posterior probability=0.9740; <0.983
- Dual: Posterior Probability=0.9908; >0.983
New Q wave MI Results:

1. The presence of a new Q wave on ECG may not be representative of a new interval Q wave MI
2. Even with the dual baseline approach, it is not clear that Q waves represent an interval MI
3. Dual baseline ECG serial read is a post hoc analysis
Effectiveness Results: 
**time to door > 2 hours**

- Ischemic events were confirmed by:
  - ECG, cardiac biomarkers, stress test, angio
- **Time-to-Door**: Time from device ST detection to presentation
- **Look-Back Window**: How many days between detection-to-presentation
  - 7-days → 90-days
- Presentation can be a protocol visit, ED visit
Time to Door > 2 hours Results: **Control**

18 events in 17 subjects

Presented > 2 hours

6 angiograms in 6 subjects

- 3 PCI
- 1 CABG
- 2 CAD 58-69%

17 events in 17 subjects

EKG: ST depression n=4
EKG: ST elevation n=1
Positive stress + EKG: ST elevation n=1
Pos. Biomarkers n=4
Positive stress test n=1
Time to Door > 2 hours Results: Control

18 events in 17 subjects

17 events in 17 subjects
Presented > 2 hours

6 angiograms in 6 subjects

• 3 PCI
  • 7.75 days
  • 4.5 days
  • 76 days

• 1 CABG
  • 3 days

• 2 CAD 58-69%
  • 5 hours, 6.5 hrs
Time to Door > 2 hours Results: Control

18 events in 17 subjects

17 events in 17 subjects
Presented > 2 hours

11 Subjects with 11 positive tests:
- EKG: ST elevation n=1
- Positive Biomarkers n=4
- Positive stress test n=1
- Positive stress + EKG: ST elev. n=1
- EKG: ST depression or T wave n=4

6 angiograms in 6 subjects
- 3 PCI
- 1 CABG
- 2 CAD 58-69%
Time to Door > 2 hours Results: Treatment

34 alarms in 27 subjects
29 alarms in 25 subjects < 2hrs
+ 5 alarms in 4 subjects >2 hrs

23 alarms in 20 subjects
• 20 angiograms in 20 subjects
  • 10 PCI & 1 thrombolytics given
  • 6 no intervention; CAD present
  • 4 negative for significant CAD (-1 received lytics)

11 alarms
• EKG: ST elevation n=2
• EKG: ST depression n=1
• Pos. biomarkers or pos. stress test n=8
Time to Door > 2 hours Results: Treatment

34 alarms in 27 subjects
29 alarms in 25 subjects < 2hrs
+ 5 alarms in 4 subjects >2 hrs

23 alarms in 20 subjects
• 20 angiograms in 20 subjects
  • 10 PCI & 1 thrombolysis given
  • 6 no intervention; CAD present
  • 4 negative for significant CAD
    (1 received lytics)

11 alarms in 10 subjects
• EKG: ST elevation n=2
• EKG: ST depression n=1
• Pos. biomarkers or pos. stress test n=8
Time to Door > 2 hours Results: Treatment

- 34 alarms in 27 subjects
- 29 alarms in 25 subjects < 2hrs
- 5 alarms in 4 subjects >2 hrs

- 1 Positive stress test
- 1 Positive enzymes
- 2 PCI*
  (*1 PCI pt had 2 alarms)
Recalculating the Combined Effectiveness Endpoint (CEE) Using 90 day window and dual ECG baseline

<table>
<thead>
<tr>
<th>Control N=446</th>
<th>Treatment N=439</th>
<th>Post. Prob. CEE</th>
<th>Endpt. Met? (&gt;0.983)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(%) CEE</td>
<td>n(%) CEE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 (6.5)</td>
<td>13 (3.1)</td>
<td>0.9908</td>
<td>Yes</td>
</tr>
<tr>
<td>25 (5.8)</td>
<td>13 (3.1)</td>
<td>0.974</td>
<td>No</td>
</tr>
<tr>
<td>24 (5.6)</td>
<td>13 (3.1)</td>
<td>0.963</td>
<td>No</td>
</tr>
</tbody>
</table>

Statistical Significance Threshold = 0.983
Recalculating the Combined Effectiveness Endpoint (CEE) Using 90 day window and dual ECG baseline

<table>
<thead>
<tr>
<th></th>
<th>Control N=446 n(%) CEE</th>
<th>Treatment N=439 n(%) CEE</th>
<th>Post. Prob. CEE</th>
<th>Endpt. Met? (&gt;0.983)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=446</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>13 (3.1)</td>
<td>0.9908</td>
<td>Yes</td>
</tr>
<tr>
<td>CEE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>13 (3.1)</td>
<td>0.974</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>24 (5.6)</td>
<td>13 (3.1)</td>
<td>0.963</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Statistical Significance Threshold = 0.983
# Time-To-Door: Key 2nd Endpoint

<table>
<thead>
<tr>
<th>Look-back Window (days)</th>
<th>Reduction in events (binary: &gt; 2hrs)</th>
<th>Reduction in time (continuous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>30</td>
<td>13 (2.9%)</td>
<td>0.9840</td>
</tr>
<tr>
<td>90</td>
<td>17 (3.8%)</td>
<td>0.9978</td>
</tr>
<tr>
<td>Treatment</td>
<td>4 (0.9%)</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical Significance Threshold = 0.975**
## Time-To-Door: Key 2\textsuperscript{nd} Endpoint

<table>
<thead>
<tr>
<th>Look-back Window (days)</th>
<th>Reduction in events (binary: &gt; 2hrs)</th>
<th>Reduction in time (continuous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>13 (2.9%)</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>17 (3.8%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>4</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>

**Statistical Significance Threshold = 0.975**
Results: STEMI

5 STEMIs; 3 treatment, 2 control

<table>
<thead>
<tr>
<th>Time to presentation</th>
<th>Treatment Group (alarm status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47 min Prior</td>
<td>Treatment (ON)</td>
</tr>
<tr>
<td>103 min Prior</td>
<td>Treatment (ON)</td>
</tr>
<tr>
<td>4 days Prior</td>
<td>Control (OFF)</td>
</tr>
<tr>
<td>15 min After</td>
<td>Treatment (ON)</td>
</tr>
<tr>
<td>13 hours After</td>
<td>Control (OFF)</td>
</tr>
</tbody>
</table>
Positive Predictive Value (PPV)

- Calculated for Treatment subjects only
- The sponsor used the same 4 ischemia tests
  - ECG, biomarkers, stress, angiogram
- The sponsor adjudicated events for PPV
  - Includes all ST changes, T wave changes
  - Includes >50% stenosis and >20% change in stenosis
  - Include non ACS events
  - Uses both site and core lab data for angios
FDA’s PPV calculation

Treatment Alarms (N = 179)

Excluded Alarms (N=72)

Aggregated Alarms (N = 15)

Remaining Alarms (N=92)

Non-confirmed Positive Event Alarms (NCPA) (N = 22+10=32)

Confirmed Positive Event Alarm (CPA) (N = 60)

Inpatient (N = 18)

Noncompliant (N = 19)

Programming Errors (N = 17)

Incomplete (N = 8)

Medical Procedure Induced (N = 9)

Algorithm Anomaly (N = 1)

Treated as CPA in Sponsor’s Calculation (N = 10)

Sleep apnea n=1

Bundle branch n=4

Vasospasm =5

31 AGEA adjudicated events + 29 sponsor adjudicated events
Treatment Alarms (N = 179)

Excluded Alarms and aggregated alarms (N=87)

Remaining Alarms (N=92)

Non-confirmed Positive Event Alarms (NCPA) (N = 22+10=32)

Confirmed Positive Event Alarm (CPA) (N = 60)

Sponsor: 70/92 = 76%
FDA: 60/92 = 65%
AGEA only: 34/92 = 37%

Treated as CPA in Sponsor’s Calculation (N = 10)
Sleep apnea n=1
Vasospasm =5
Bundle branch n=4

AGEA adjudicated events + sponsor adjudicated events
Treatment Alarms (N = 179)

Excluded Alarms and aggregated alarms (N=87)

Remaining Alarms (N=92)

Non-confirmed Positive Event Alarms (NCPA) (N = 22+10=32)

Confirmed Positive Event Alarm (CPA) (N = 60)

Treated as CPA in Sponsor’s Calculation (N = 10)
  - Sleep apnea n=1
  - Vasospasm =5
  - Bundle branch n=4

AGEA adjudicated events + sponsor adjudicated events

Sponsor: 70/92=76%
FDA: 60/92=65%
AGEA only: 34/92=37%

PPV calculation
False Negative Rate

• Unable to truly calculate the FNR
• $\text{FNR} = \frac{\text{FN}}{\text{FN} + \text{TP}}$
• Treatment Group:
  23 angiograms for symptoms
  $\text{FNR} = \frac{23 + X}{(23 + X) + 34} \geq 40\%$
• This is a guestimate, but should not overestimate the true FNR
Indications for Use (IFU)

The Guardian System is indicated to alert patients with prior acute coronary syndrome events, to ST segment changes indicating acute coronary occlusion.

Guardian System alerts reduce the overall time-to-door from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.

Panel Question:
The panel will be asked if the ALERTS results support the proposed IFU and indicated patient population
Clinical Conclusions

1. The safety endpoint was met

2. The primary effectiveness endpt. was not met when using a 90 day window and the pre-specified ECG analysis

3. The primary effectiveness endpt. was met when using a 90 day window and a dual baseline ECG analysis
   a. This ECG analysis is post hoc
   b. Endpoint no longer met when 4 events are removed from the analysis
Clinical Conclusions

- Clinical utility is clearly demonstrated in some subjects.
- However, many ST detections appear to correspond to possible ischemia in absence of ACS event.
- Patients respond to the alarm; Benefit of alarm may depend on whether an acute ACS event is ongoing.
FDA Presentations

- Introduction – LTJG Stephen Browning
- Statistical Presentation – Dr. Zhiheng Xu, PhD
- Clinical Presentation – Dr. Kimberly Selzman, MD
- Conclusion – LTJG Stephen Browning
Post Approval Study (PAS)

- Prospective
- Event driven
- Registry
- Sponsor proposes to collect:
  - Time-to door for qualified events
  - Patient emergency alarm compliance
  - PPV
  - Measure EF at baseline and post ACS
  - Safety data for implant and replacement
FDA Conclusions

• Primary Safety Endpoint was met
• Primary Effectiveness Endpoint was not met
• Trial conduct and data analysis issues make clinical and statistical interpretation of the results difficult