Overview of the 2016 US Food and Drug Administration Circulatory System Devices Panel Meeting on the AngelMed Guardian System

On March 16, 2016, the US Food and Drug Administration (FDA) convened a meeting of the Circulatory System Devices Panel to consider a premarket approval application for the AngelMed Guardian System based on the results of the pivotal ALERTS trial (AngelMed for Early Recognition and Treatment of STEMI) (URL: http://www.clinicaltrials.gov. Unique identifier: NCT00781118). The system comprises an implantable device similar to a single-chamber pacemaker, an external device that the patient carries, and a physician console. The device analyzes ST-segment shift through a single active-fixation lead in the right ventricular apex. If ST shift is identified, then the implantable device vibrates and the external device flashes and sounds an auditory alarm.

HIGHLIGHTS FROM THE SPONSOR’S PRESENTATION

More than 1 in 3 acute myocardial infarctions occur without chest pain, most commonly in women, diabetic patients, and the elderly. ST shift occurs rapidly in humans following coronary balloon occlusion.1 The AngelMed Guardian aims to reduce time to presentation by alerting the patient to ST shift even in the absence of symptoms. The ALERTS trial tested the safety and effectiveness of the Guardian System. A Bayesian adaptive design was used to adjust sample size based on interim treatment effect. The trial enrolled high-risk patients with a history of coronary artery disease (97% had previous revascularization). The trial was stopped early because of concerns that the predictive model did not accurately account for new Q waves. Nine hundred ten patients had the Guardian implanted (451 in the treatment arm versus 456 in the control arm with the device deactivated). Study duration was 6 months to allow patients in the control arm the benefit of alerts after 6 months.

Thirty patients experienced a total of 31 complications (11 device-related infections and 8 system extractions). This resulted in a complication-free rate of 96.7%, meaning the primary safety end point was met. There were 6 deaths, of which 4 were from cardiac or unexplained causes. Interrogation of the device after death revealed that all 4 had detected events before death.

The primary effectiveness end point was a composite of late presentation for confirmed events (time to presentation >2 hours), new Q waves at 6 months, and cardiac or unexplained death. Per protocol, only 1 ECG served as the baseline against which new Q waves were adjudicated. Post hoc analysis using 2 baseline ECGs reduced the number of adjudicated Q waves in both treatment and control arms. Also, per protocol, late presentations were only counted for alerts occurring in the 7 days before a confirmed event. Post hoc analysis with an extended 90-day window increased the number of late presentations in the control arm. The primary effectiveness end point was only met by combining these 2 post hoc analyses (Table). Eighty-five percent of presentations occurred within 2 hours in the treatment arm in comparison with 6% in the control arm. All 5 ST-segment–elevation myocardial infarctions in the ALERTS trial had an associated Guardian alert, and 4 had symptoms;

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however, 23 acute coronary syndrome (ACS) events did not trigger alerts.

**HIGHLIGHTS FROM THE FDA PRESENTATION**

The FDA viewed early trial termination despite interim analyses, suggesting that enrollment should continue as a major protocol violation. The primary effectiveness end point was only met after post hoc analyses. However, with the use of more standard definitions of ACS, once again the end point failed to meet statistical significance (Table). The FDA cautioned that post hoc analyses could lead to false declaration of significance and spurious inferences. Furthermore, excluding subjects without definite ACS resulted in a recalculated primary effectiveness end point that, once again, did not reach statistical significance. The secondary end point of reduction in time to presentation reached statistical significance (2.7 versus 52.3 hours, treatment versus control arms). Forty percent of alerts were excluded from the positive predictive value analysis; therefore, the best possible positive predictive value was 65%. However, by using more stringent adjudication committee-confirmed ACS, the positive predictive value was only 37%. The false-negative rate could not be calculated accurately because of incomplete data, but the FDA estimated a false-negative rate of 40%.

**PUBLIC HEARING**

Patient testimonials highlighted how the device identified acute myocardial infarctions despite the absence of symptoms. Representatives of patient support organizations emphasized the importance of peace of mind for patients who have had an acute myocardial infarction. However, the panel was concerned that the device could confer a false sense of security if it failed to detect ST shift and patients interpreted lack of alert as a green light to ignore symptoms.

**PANEL DELIBERATIONS**

The Bayesian framework of the ALERTS trial made it difficult to adjust for changes in methodology. The panel questioned whether a trial terminated for design and conduct issues had sufficient integrity to warrant regulatory approval.

Only 47% of ACS events in the treatment arm were cardiac enzyme positive, the remainders were new Q waves or positive stress tests. Many events were non-

**Table. Analysis of the Primary Effectiveness End Point**

<table>
<thead>
<tr>
<th>Number of Days Before Confirmed Events for the Definition of Late Presentation</th>
<th>Number of ECGs Serving as Baseline for Adjudication of New Q Waves</th>
<th>Control n (%)</th>
<th>Treatment n (%)</th>
<th>FDA Comments</th>
<th>Posterior Probability</th>
<th>End Point Met? (&gt;0.983)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1</td>
<td>21 (4.9)</td>
<td>16 (3.8)</td>
<td>Original protocol-specified primary effectiveness end point</td>
<td>0.7856</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>20 (4.7)</td>
<td>13 (3.1)</td>
<td>Post hoc analysis using 2 rather than 1 baseline ECG to adjudicate new Q waves</td>
<td>0.8833</td>
<td>No</td>
</tr>
<tr>
<td>90</td>
<td>1</td>
<td>29 (6.8)</td>
<td>16 (3.8)</td>
<td>Post hoc analysis using a window of 90 rather than 7 days for the definition of late presentation</td>
<td>0.9740</td>
<td>No</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
<td>28 (6.5)</td>
<td>13 (3.1)</td>
<td>Combination of 2 post hoc analyses: extended 90-day window and 2 baseline ECGs</td>
<td>0.9908</td>
<td>Yes</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
<td>25 (5.8)</td>
<td>13 (3.1)</td>
<td>FDA excluded 3 patients with ST-segment depression or T-wave abnormalities (did not meet standard definition of ACS)</td>
<td>0.974</td>
<td>No</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
<td>24 (5.6)</td>
<td>13 (3.1)</td>
<td>FDA excluded 1 patient with positive nuclear stress test but negative angiogram (did not meet standard definition of ACS)</td>
<td>0.963</td>
<td>No</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; and FDA, US Food and Drug Administration.
ST-segment–elevation myocardial infarctions for which time to presentation might not be as important a predictor of outcomes as with ST-segment–elevation myocardial infarctions. The panel was particularly concerned about false negatives leading patients to ignore chest pain because their device did not alarm.

The panel noted that the risks included both acute and chronic risks of an implanted device, and emphasized that false-positive alerts could lead to unnecessary tests with additional risks. For example, 12 patients with alerts but no symptoms underwent coronary catheterization, which revealed normal coronary arteries. The ALERTS trial did not capture the number of additional tests performed as a result of false-positive alerts.

The Sponsor proposed the following indications for use:

1. 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 presentation from a detected acute coronary occlusion until presentation at a medical facility independent of patient-recognized symptoms.

The panel clarified that the device should be considered only in high-risk patients, because this was the population studied in the ALERTS trial. The panel was doubtful that a secondary end point should be used in the proposed indications because the primary effectiveness end point was not met. Postapproval plans including a physician education program and prospective registry were considered acceptable.

**FINAL VOTE**

Many members of the panel recognized the unmet clinical need for devices to improve recognition of silent acute myocardial infarctions, expressing both enthusiasm for the AngelMed technology and concern over the results of the ALERTS trial. After careful deliberations, the panel voted:

a. Concerning the safety of the AngelMed Guardian System, the panel voted against (4:8). Panel members highlighted that the risks of the device were not just those of the implantation, but also the risks of additional tests triggered by false-positive alerts.

b. Concerning the effectiveness of the AngelMed Guardian System, the panel voted unanimously against (0:12) accepting the effectiveness data presented by the Sponsor, citing concerns with trial conduct and statistical analysis and the high number of patients with ACS events that were not recognized by the device.

c. The panel voted unanimously (0:12) that the benefits of the AngelMed Guardian System did not outweigh the risks and therefore recommended against approving the premarket approval application.

It will be interesting to see how the Sponsor and the FDA proceed, in particular, whether further clinical studies, perhaps focused on reduction of Q-wave infarctions, will be performed to support another premarket approval application.

**DISCLOSURES**

Dr Waksman is a Consultant: Abbott Vascular, Biotronik, Boston Scientific, Medtronic, St. Jude Medical; Speakers Bureau: AstraZeneca, Boston Scientific, Merck; Grant Support: AstraZeneca, Biotronik, and Boston Scientific.

All other authors report no disclosures.

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**FOOTNOTES**

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**REFERENCES**

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