

FDA Executive Summary

Prepared for the
May 6, 2014 meeting of the
Circulatory System Devices Panel

P110024
ResQTrial
ResQCPR™ System (ResQPOD® and ResQPump®)
Advanced Circulatory Systems, Inc.

Introduction

This is the FDA Executive Summary for the ResQCPR™ System (ResQPOD® and ResQPump®), that was utilized in the ResQTrial to evaluate survival and neurological outcome in patients suffering from out-of-hospital non-traumatic cardiac arrest. The ResQCPR™ System is comprised of two devices, the ResQPOD® (impedance threshold device [ITD]) and the ResQPump® (a compression/decompression manual CPR pump), and is indicated for use in the performance of CPR to increase survival with favorable neurologic function in patients with non-traumatic cardiac arrest.

A “run-in” or training phase of the study was approved by the agency on April 21, 2005 under IDE G050062. The pivotal phase of this trial was approved on October 27, 2005 under the same IDE number. The ResQTrial was performed under 21 CFR 50.24 Exception from informed consent requirements for emergency research. Advanced Circulatory Systems, Inc., has most recently submitted a Premarket Approval Application (PMA) for marketing approval of the System (P110024). This submission has been reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA’s review of the PMA, highlighting the particular areas for which we are seeking your expertise and input. These topics will include:

- the proposed indications for use;
- the results of the clinical study conducted by the Sponsor; and
- trial conduct issues.

At the conclusion of your review and discussion of the data presented, FDA will ask for your recommendation regarding whether or not the data demonstrate a reasonable assurance of safety and effectiveness.

Executive Summary Overview

Study Design

The ResQTrial (G050062) was a prospective, randomized, multi-center trial performed to evaluate the safety and effectiveness of the ResQCPR™ System in patients with non-traumatic, out-of-hospital cardiac arrest. The ResQTrial underwent several study design modifications over the course of the trial, but ultimately generated data to evaluate CPR when using the System's two components (an active compression-decompression pump [ACD] and an impedance threshold device [ITD]), as compared to standard CPR (s-CPR) alone. The study was performed under 21 CFR 50.24 Exception from Informed Consent Requirements for Emergency Research, and patients were randomized to receive either standard CPR or CPR with both devices (ACD-ITD), and the primary endpoint was survival to discharge with good neurologic outcome (defined as a modified Rankin Score (mRS) ≤ 3).

The analysis populations included the intention to treat (ITT - all enrolled subjects meeting initial inclusion/exclusion criteria – supplementary analysis set) and a modified ITT (mITT – subjects who meet both initial and final inclusion/exclusion criteria – primary analysis set). Final inclusion/exclusion criteria included items that cannot be readily determined before therapy is to be applied, e.g., DNR orders.

The study was to enroll 2696 patients (1348 in each arm), however enrollment was suspended in July 2009 (after 61% of anticipated enrollment 1655/2696), and ultimately terminated in April 2010, due to lack of funding, according to the sponsor.

Study conduct issues

FDA believes that “effective unblinding” of the sponsor occurred since 2006. “Effective unblinding” is defined in the following manner: at a minimum, knowledge of the treatment group difference by the sponsor and use of this knowledge to impact trial decisions and/or execution. Any changes to the trial after effective unblinding will bias the trial, destroy the stringent control of Type I error and render any subsequent p-value analysis unquantifiable. Interpretation of trial results, therefore, becomes problematic.

Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

During the course of the PMA review, it was noted that retrospective revisions were made to case report forms, which included changes to endpoint values (mRS values) and late patient exclusions from the mITT analysis, which appeared to alter conclusions concerning device effectiveness. This led FDA to question how the trial was conducted, monitored, and how the data were managed. Specific areas of concern include:

- How §50.24 Exception of Informed Consent for Emergency Research was applied; *FDA believes that some study data that should have been collected, was not, possibly due to misunderstanding of the waiver of informed consent regulation;*
- FDA- approved trial modifications; *unplanned trial design and statistical plan modifications were formulated following knowledge of outcomes by treatment groups available to the sponsor;*
- potential complete unblinding; *the sponsor received reports from the DSMB as early as 2006 containing data tables which contained encrypted treatment specific results data, effectively unblinding them; additionally, FDA believes these results could readily and accurately be un-encrypted, although the Sponsor denies that it became inappropriately unblinded to aggregate data during the study.*
- trial monitoring; *Data Coordinating Center (DCC) members/study monitors were company officials and had access to individual case report forms, and developing data and trial results by encrypted groups as provided in DSMB reports; and*
- data management; *case report forms were revised out to 3 ½ years after the index event, leading to changes to mRS values and changes to the mITT population (the sponsor cites using the 2008 FDA Guidance document titled Data Retention when Subject Withdraw from FDA-Regulated Clinical Trials).*

The detailed Executive Summary discusses these areas of concern, but in general, sponsor effective unblinding may have informed decisions to 1) modify the study design, 2) retrospectively revise patient case report forms, i.e., modifying mRS values and patient exclusion criteria with a net outcome in favor of the test arm, and 3) stop the trial early. These issues need to be considered in light of the dataset presented for a determination of safety and effectiveness for the ResQCPR™ System. Please note that the sponsor has denied that it became inappropriately or completely unblinded to aggregate data during the study.

Primary Endpoint, Secondary Endpoint, and Additional Analyses

As will be discussed in more detail in the body of the Executive Summary, the original trial was set up as a three-arm trial with an s-ITD arm. In order to address multiple testing issues for the primary endpoint, a two-sided alpha of 0.022 was initially specified for the final analysis before the s-ITD arm was dropped. After dropping the s-ITD arm, FDA approved the change of the alpha level to 0.049 (two-sided). FDA came to understand the above study issues' ramifications for type I error inflation during the PMA review process. One needs to be cautious in interpreting any analysis result which may have been affected by alpha inflation issues. As such, in order to partially address our inflation concerns, FDA believes it informative to consider the trial results in the context of the original alpha level of 0.022 (two-sided). FDA acknowledges that doing so is a post-hoc approach, but further points out that it may be impossible to accurately quantify the magnitude of the alpha inflation.

The final mITT population did not include the following patients, 1) 28 patients adjudicated late and removed from the mITT population for etiology, and 2) 163 medication/drug overdose patients. Additionally, since there was no pre-specified plan for imputation, the

primary mITT analysis also excludes 17 patients [13 s-CPR, 4 ACD-ITD] with missing endpoint values.

To further examine the potential biases introduced by the trial modifications, both the sponsor and the FDA performed the primary endpoint analysis using two additional approaches.

Approach 1 (first enrolled 1400)

- analyze the first enrolled 1400 subjects, assuming the study design had not been modified

Approach 2 (inverse normal method)

- analyze all subjects using an inverse normal method (CHW method) - the CHW (Cui-Hung-Wang) is a common inverse normal method used to combine data from two stages of a trial into a single test statistic for p-value testing.

Primary Endpoint

The Primary Endpoint was defined as Survival to Hospital Discharge with MRS ≤ 3

Table 4 Survival to Hospital Discharge with MRS ≤ 3 (mITT) complete case, (calculated by sponsor)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------------|-----------------|-----------------|------------------------|
| mITT analysis[#] | 5.88% (47/800) | 8.95% (75/838) | 0.0186 |
| First 1400 subjects | 6.0% (41/684) | 9.1% (64/704) | 0.033 |
| CHW | 5.88% (47/800)* | 8.95% (75/838)* | 0.029** |

[#]: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Primary endpoint was met for the complete case analysis at an alpha level of 0.049.

Table 5. Survival to Hospital Discharge with MRS \leq 3 (ITT) complete case, (calculated by sponsor)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|---|---------------------|----------------------|------------------------|
| ITT analysis# | 5.99% (71/1186) | 8.00% (101/1262) | 0.057 |
| First 2041 subjects^{##} | 5.85% (58/991) | 8.23% (85/1033) | 0.038 |
| CHW | 5.99% (71/1186)* | 8.00% (101/1262)* | 0.066** |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

^{##} Parent ITT population to “First 1400” mITT subjects

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

The primary endpoint was not met for the complete case ITT analysis at an alpha level of 0.049. The nominal p-value for the first 2041 ITT subjects was less than an alpha level of 0.049, but the primary endpoint was not met ($p > 0.049$) using the CHW approach. The ITT population includes all patients enrolled, including those excluded from the mITT population (e.g., medication/drug overdose, non-cardiac etiologies, etc.), and is important because in general clinical practice, FDA believes that the ability to distinguish cardiac arrest etiologies is unlikely

Secondary Endpoints

The pre-specified secondary safety endpoint of major adverse events was met. The pre-specified secondary effectiveness endpoints evaluating Cognitive Abilities Screening Instrument (CASI) at 90 days and 1 year post-cardiac arrest in surviving subjects were not met.

Additional Analyses

As-Treated

Taking into consideration the study conduct concerns mentioned above FDA was concerned about the robustness of treatment results. The following additional analyses were performed to examine the robustness of the results.

Table 2. Number of Patients with Study Devices Used by Study Group, mITT (by the sponsor)

| Number of devices used | S-CPR (N=813) | ACD-ITD (N=842) |
|------------------------|---------------|-----------------|
| 0 | 803 | 28 |
| 1 (1 ITD or 1 ACD) | 5 | 32 |
| 2 (1 ITD and 1 ACD) | 5 | 782 |

The sponsor used three methods to perform the as-treated analysis:

Method 1

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with a least "1" device, either ACD, ITD, or both (n = 782+32 = 814)

Method 2

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with both ACD and ITD devices (n = 782)

Method 3

- All Subjects, regardless of randomization assignment, re-classified as having received s-CPR with "0" devices (n=803+28=831) or having received ACD-ITD with "2" devices (n782+5=787).

Table 11. Survival to Hospital Discharge with MRS \leq 3, As-Treated Analysis (Complete Case) (By the sponsor)

| Method# | s-CPR | ACD-ITD | 2-sided p-value |
|-----------|---------------|---------------|-----------------|
| Method 1: | 5.9% (47/790) | 8.3% (67/811) | 0.080 |
| Method 2: | 5.9% (47/790) | 8.1% (63/779) | 0.113 |
| Method 3: | 6.7% (55/817) | 8.0% (63/784) | 0.339 |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

FDA defined a fourth As-Treated method which compared the ACD-ITD “mITT” population to a s-CPR “no device” population:

Method 4

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- all ACD-ITD subjects, irrespective of devices actually used (n=782+32+28=842).

The as-treated methods were analyzed using alpha control approaches previously defined (First 1400 and CHW). The sponsor analyzed the first three methods; FDA analyzed four as-treated methods.

Table 12. Survival to Hospital Discharge with MRS ≤ 3, As-Treated Analysis (Complete Case) (By FDA)

| Approach | Method | S-CPR | ACD-ITD | 2-sided p-value |
|---------------------|-----------|---------------------|---------------------|-----------------|
| First 1400 subjects | Method 1 | 6.07% (41/675) | 8.50% (58/682) | 0.0949 |
| | Method 2: | 6.07% (41/675) | 8.24% (54/655) | 0.1364 |
| | Method 3: | 6.74% (47/697) | 8.19% (54/659) | 0.3518 |
| | Method 4: | 6.07% (41/675) | 9.09% (64/704) | 0.0419 |
| CHW approach | Method 1: | 5.95% (47/790) * | 8.26% (67/811) * | 0.1060** |
| | Method 2: | 5.95% (47/790) * | 8.09% (63/779) * | 0.1480** |
| | Method 3: | 6.73% (55/817) * | 8.04% (63/784) * | 0.4250** |
| | Method 4: | 5.95% (47/790) * | 8.95% (75/838) * | 0.0342** |

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

As-Treated Analyses (mITT)

In FDA’s As-Treated analyses addressing alpha inflation, the treatment arm did not demonstrate statistical superiority in the first three methods. In FDA’s method 4, which compared the ACD-ITD “mITT” population to a s-CPR “no device” population, for complete cases the nominal p-value was less than the two-sided alpha of 0.049.

Missing Data

The rate of missing data in the s-CPR arm (1.6%, 13/813) was three times that found in the ACD-CPR+ITD arm (0.5%, 4/842) in terms of the primary endpoint (i.e., 17 patients had missing primary endpoint data).

The FDA performed sensitivity analyses using as-treated analysis under a best-case scenario. Under the best-case scenario, all the missing values in the ACD-ITD arm are imputed as $mRS \leq 3$ while all the missing values in the s-CPR arm are imputed as $mRS \geq 3$.

Table 14. Survival to Hospital Discharge with $MRS \leq 3$, Best Case Analysis for as-treated population (By FDA)

| Approach | Method | S-CPR | ACD-ITD | 2-sided p-value |
|---------------------|----------|--------------------|--------------------|-----------------|
| First 1400 subjects | Method 1 | 5.99% (41/684) | 8.77% (60/684) | 0.0623 |
| | Method 2 | 5.99% (41/684) | 8.52% (56/657) | 0.0912 |
| | Method 3 | 6.65% (47/707) | 8.47% (56/661) | 0.2191 |
| | Method 4 | 5.99% (41/684) | 9.48% (67/707) | 0.0162 |
| CHW | Method 1 | 5.85% (47/803)* | 8.60% (70/814)* | 0.0500** |
| | Method 2 | 5.85% (47/803)* | 8.44% (66/782)* | 0.0712** |
| | Method 3 | 6.62% (55/831)* | 8.39% (66/787)* | 0.2442** |
| | Method 4 | 5.85% (47/803)* | 9.38% (79/842)* | 0.0116** |

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

In the first three As-Treated (best case scenario) analyses, the treatment arm did not demonstrate statistical superiority. Only Method 4 (best case scenario), which compared the ACD-ITD “mITT” population to a s-CPR “no device” population yielded a nominal p-value less than an alpha of 0.049.

FDA performed a tipping point analysis to evaluate the robustness of the superiority conclusion under method 4. The tipping point analysis replaced missing data with values to determine the point at which the study conclusion becomes altered (see Section 6.2 Study Results). As can be seen FDA found the superiority conclusion in method 4 to be sensitive to the missing data and very sensitive particularly when considering the possibility of alpha inflation.

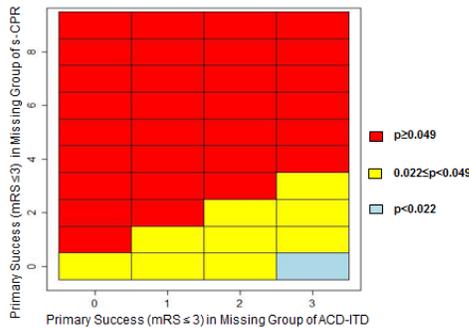


Figure 6.2.1 Tipping Point Analysis for As-Treated Analysis Method 4 First 1400 mITT subjects

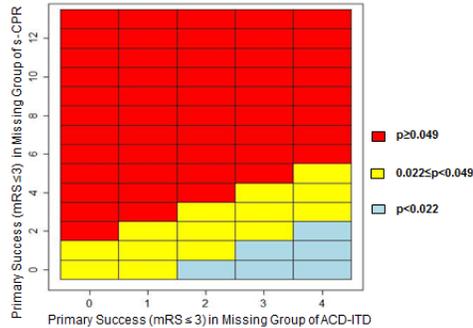


Figure 6.2.2 Tipping Point Analysis for As-Treated Analysis Method 4 CHW approach

Missing data

Superiority was not demonstrated in as-treated analysis Methods 1-3 under the best case scenario. The nominal p-values were less than an alpha of 0.049 in Method 4, but the analysis was found to be sensitive to the missing data and very sensitive particularly when considering the possibility of alpha inflation

Medication/Drug Overdose

To investigate the impact of these excluded overdose subjects had on the analysis results, we added these 163 subjects in the mITT and as-treated analyses.

Table 19 (Appendix 3). Survival to Hospital Discharge with MRS ≤ 3, mITT/as-treated plus drug overdose subjects (Complete Case) (by the FDA)

| Analysis Population | Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------|------------------------------------|--------------------|--------------------|------------------------|
| mITT | All S-CPR vs. ACD-ITD [#] | 6.59% (57/865) | 8.98% (84/935) | 0.0652 |
| | First 1400 subjects | 6.82% (47/689) | 9.46% (66/698) | 0.0776 |
| | CHW | 6.59% (57/865)* | 8.98% (84/935)* | 0.0882** |
| As-Treated Method 1 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.30% (75/904) | 0.2057 |
| | First 1400 subjects | 6.91% (47/680) | 8.88% (60/676) | 0.1912 |
| | CHW | 6.67% (57/855)* | 8.30% (75/904)* | 0.2624** |
| As-Treated Method 2 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.20% (71/866) | 0.2336 |
| | First 1400 subjects | 6.91% (47/680) | 8.63% (56/649) | 0.2598 |
| | CHW | 6.67% (57/855)* | 8.20% (71/866)* | 0.3172** |
| As-Treated Method 3 | All S-CPR vs. ACD-ITD [#] | 7.45% (66/886) | 8.15% (71/871) | 0.5946 |
| | First 1400 subjects | 7.55% (53/702) | 8.58% (56/653) | 0.5489 |
| | CHW | 7.45% (66/886)* | 8.15% (71/871)* | 0.7212** |
| As-Treated Method 4 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.98% (84/935) | 0.0788 |
| | First 1400 subjects | 6.91% (47/680) | 9.46% (66/698) | 0.0951 |
| | CHW | 6.67% (57/855)* | 8.98% (84/935)* | 0.1024** |

[#]: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

^{*}: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

^{**}: two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Medication/Drug Overdose
 Superiority was not met when OD patients are included in either the mITT or the as-treated analyses

Delayed Adjudication of 28 Patients

To investigate the impact on the study conclusion of the 28 subjects removed from the mITT analysis based on late adjudication of cardiac arrest etiology, these 28 subjects were added to the mITT and as-treated analyses:

Table 20 (Appendix 3). Survival to Hospital Discharge with MRS ≤ 3, mITT plus 28 delayed adjudicated subjects (Complete Case) (by the FDA)

| Analysis Population | Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------|---------------------|--------------------|--------------------|------------------------|
| mITT | S-CPR vs. ACD-ITD# | 6.20% (50/806) | 8.84% (76/860) | 0.0512 |
| | First 1400 subjects | 6.48% (44/679) | 9.17% (65/709) | 0.0722 |
| | CHW | 6.20% (50/806)* | 8.84% (76/860)* | 0.0642** |
| As-Treated Method 1 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.17% (68/832) | 0.1520 |
| | First 1400 subjects | 6.57% (44/670) | 8.59% (59/687) | 0.1826 |
| | CHW | 6.28% (50/796)* | 8.17% (68/832)* | 0.1966** |
| As-Treated Method 2 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.03% (64/797) | 0.2062 |
| | First 1400 subjects | 6.57% (44/670) | 8.35% (55/659) | 0.2504 |
| | CHW | 6.28% (50/796)* | 8.03% (64/797)* | 0.2534** |
| As-Treated Method 3 | S-CPR vs. ACD-ITD# | 7.04% (58/824) | 7.98% (64/802) | 0.5102 |
| | First 1400 subjects | 7.23% (50/692) | 8.30% (55/663) | 0.4782 |
| | CHW | 7.04% (58/824)* | 7.98% (64/802)* | 0.6042** |
| As-Treated Method 4 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.84% (76/860) | 0.0518 |
| | First 1400 subjects | 6.57% (44/670) | 9.17% (65/709) | 0.0892 |
| | CHW | 6.28% (50/796)* | 8.84% (76/860)* | 0.0752** |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Inclusion of the removed 28 patients (based on delayed adjudication) in mITT and as-treated analyses

Device superiority was not met in either the mITT analyses or the as-treated analysis

FDA notes a trend for clinical effectiveness of the ACD-ITD device, as demonstrated by the point estimates of success in the tables above. FDA will be seeking the panel's interpretation of this apparent effectiveness signal in the context of FDA's study conduct concerns.

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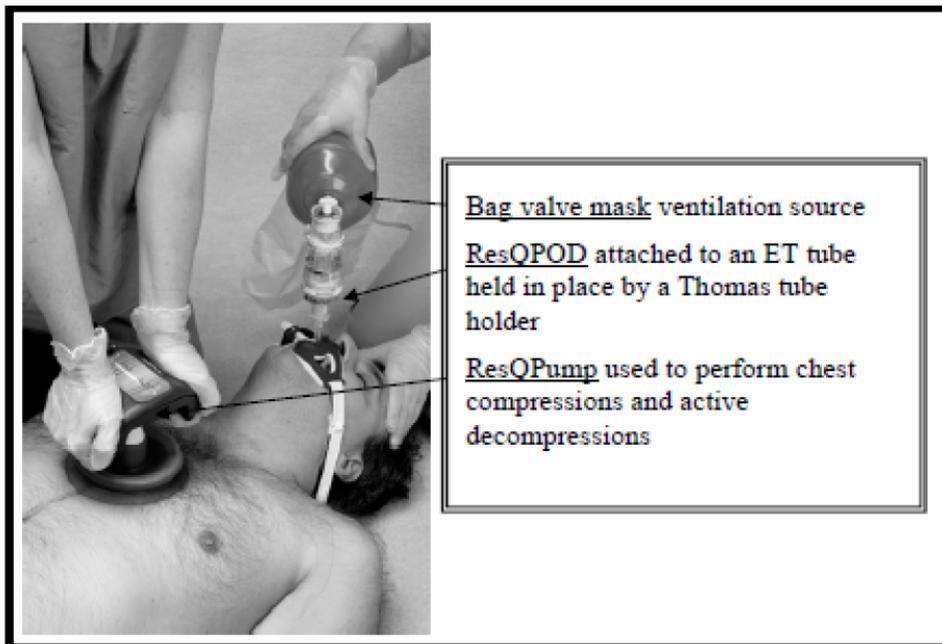
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1 DEVICE DESCRIPTION

The ResQCPR™ System is comprised of two devices: **The ResQPOD® 16.0 Impedance Threshold Device (ITD)**, and the **ResQPump® Active Compression Decompression CPR (ACD-CPR) Device**. These devices are used together during manual CPR in an attempt to enhance venous return to the heart and blood flow to vital organs during CPR to ultimately increase survival and neurologic outcome in patient suffering from out of hospital cardiac arrest.



Picture taken from P110024

The concept behind the use of these devices is that cardiac output from standard CPR (S-CPR) may be limited by venous return to the heart during the passive decompression phase. By actively decompressing the heart, the ResQPump® (ACD-CPR device) may be able to create a greater increase in negative intrathoracic pressure, possibly resulting in greater venous return and thereby promoting increased cardiac output during the next active compression phase.

However, the greater increase in negative intrathoracic pressure is diminished by the influx of air into the chest during the decompression phase. As a result, some of the potential hemodynamic benefit of active decompression may be lost. The ResQPOD® (inspiratory ITD – impedance threshold device) contains a pressure sensitive valve that impedes the influx of gas during chest wall decompression, helping to maintain the intrathoracic vacuum. As such, active ventilation may not be impeded.

1.1 ResQPOD® ITD 16.0

Shown below on an endotracheal tube and a face mask [pictures taken from P110024]:



Figure 1 ReQPOD

The ResQPOD® 16.0 ITD is a non-sterile, single-use, disposable device that is inserted in the respiratory circuit (during cardiopulmonary resuscitation [CPR]) between the patient (via a facemask or an advanced airway) and the ventilation source (e.g., bag-valve or demand-valve resuscitators, a rescuer's mouth, or an automated ventilator). It consists of a ventilation port, an airway port, timing lights and a diaphragm. The diaphragm selectively prevents air/oxygen from being drawn into the chest during the chest decompression phase of CPR. Timing lights provide a guide to maintain the recommended ventilation rate (10 ventilations/minute). The ITD includes a safety check valve mechanism that allows the patient to breathe in through the ITD if the patient gasps or has a return of spontaneous circulation (ROSC).

1.2 ResQPump®



Figure 2: Active Compression Decompression CPR



Figure 2a: Device (ResQPump)



Figure 2b. Holding the ACD-CPR Device



Figure 2c. Compression Phase

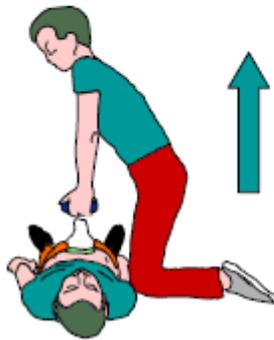


Figure 2d. Decompression Phase

The ResQPump® is a reusable device which includes a suction cup (applied to the patient’s chest), a handle, a force gauge (for compressions and decompression), and a metronome. The rescuer applies standard, manual CPR via the device handle, however, due to the suction cup, decompression of the chest wall is active in that the rescuer pulls up on the handle following the chest compression. A force gauge provides feedback to the rescuer indicating the force applied during compression and decompression (correlating to an appropriate compression depth). An audible metronome (80 cycles/minute) provides a guide to maintain the compression/decompression rate.

2 PROPOSED INDICATIONS FOR USE

The ResQCPR™ System is intended for use in the performance of CPR to increase survival with favorable neurologic function in patients with non-traumatic cardiac arrest.

The study was performed in adult patients age 18 and older. The sponsor has not placed an age or size limit in their indications for use statement. FDA will ask the panel to discuss the appropriateness of the indications for use.

3 PRE-CLINICAL AND ANIMAL STUDIES

The sponsor has conducted bench testing and provided information about animal studies for the ResQCPR™ System and/or the individual components of the System (ResQPOD® and

ResQPump®). The following information was provided, reviewed by FDA, and found to be acceptable:

3.1 Pre-Clinical Studies

- **Bench testing** inclusive of performance related testing, e.g., structural integrity testing, battery integrity and life, and measurement/timing accuracy*, have been performed for the current design. All testing has been reviewed and deemed acceptable for the intended use of the device(s). **The accuracy of the timing mechanism for the ResQPOD® had an overall failure rate of approximately 7%. The sponsor indicates that the timing mechanism is meant more as a reminder, and that failure of the timing mechanism should not affect CPR therapy since the emergency responder should be able to rely on their training to perform the therapy at the appropriate rate.*
- **Biocompatibility** testing has been performed on both devices and is compliant with FDA recognized international standards for biocompatibility appropriate for this type of device.
- **Sterilization** is not applicable to the ResQCPR™ System, as the System is not provided sterile. The ResQPOD® is a single use, disposable device and is cleaned and packaged to prevent contamination. The ResQPump® is a reusable device and adequate cleaning/disinfecting information is provided in the labeling.
- **Shelf-life** of 4 years has been validated for the ResQPOD® (accelerated aging studies); adequate information related to device cleaning/disinfecting, calibration of the force gauge, and evaluation of the suction cup (for replacement) has been provided for the reusable ResQPump® in place of a shelf-life.
- Test results demonstrating that the device is compliant with FDA recognized international standards for **electrical safety and electromagnetic compatibility**.
- Complete **software** documentation, including test results from complete software verification and validation testing demonstrating acceptable performance.

3.2 Animal Studies

Prospective animal data were not provided for the implementation of this study due to the significant US and/or OUS clinical data available for both of these devices (see Pre-PMA Marketing History, Section 3.1 above).

The sponsor did identify several animal studies (non-GLP) that had been performed on the devices (ITD) or device types (automated ACD), both separately and together as a system, in addition to the clinical data available for these devices, to support the pre-clinical/in-vivo requirements for G050062. The overall conclusions from these studies suggested that the lower intrathoracic pressures generated by the combination of the ACD and ITD devices generated greater blood blows to both the heart and brain (due to lower intrathoracic and

intracranial pressures).

4 REGULATORY and CLINICAL USE HISTORY

4.1 Pre-PMA Marketing/Regulatory History

ResQPOD®

ResQPOD ITD 16.0 (inspiratory threshold of -16mmH₂O – *used in the ResQTrial*)

(a) CE Mark - The ResQPOD® ITD 16.0 is currently marketed in Europe. Specifically, the ResQPOD® ITD 16.0 (the version used in the ResQTrial G050062, and in this PMA), includes a safety check valve that allows inspiration at -16cm H₂O. This check valve is a design safety feature in the event that the patient begins to breathe independently while the device is in place within the airway circuit. CE marketing for the -16cm H₂O ResQPOD® was received on February 14, 2003 with the following indication:

“The ResQPOD® Impedance Threshold Device is indicated for use in the treatment of adult patients with cardiac arrest (absence of breathing and absence of circulation indicators).”

(b) ROC PRIMED Study - This ResQPOD® ITD 16.0 alone was utilized in the National Institute of Health (NIH)/National Heart Lung and Blood Institute (NHLBI) sponsored Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation using an Impedance valve and Early vs. Delayed Analysis (PRIMED) Study – a randomized, double-blind trial of the ResQPOD ITD vs. sham. The ROC PRIMED Study also simultaneously investigated an Analyze Later (300 compressions of CPR before evaluating the rhythm) vs. Analyze Early (approximately 50 compressions before evaluating the rhythm). The ROC PRIMED study was performed under §50.24 permitting waiver of informed consent for emergency research. 16,542 patients were enrolled into the study.

The ROC PRIMED Study enrolled over 10,000 patients into the ITD part of the study. The trial was voluntarily terminated by ROC after approximately 2 ½ years of enrollment on the recommendation of the trial’s DSMB and sponsoring agency, which had concluded futility for both factors of the study. The published results for this halted study were:

Of 8718 patients included in the analysis, 4345 were randomly assigned to treatment with a sham ITD and 4373 to treatment with an active device. A total of 260 patients (6.0%) in the sham-ITD group and 254 patients (5.8%) in the active-ITD group met the primary outcome (risk difference adjusted for sequential monitoring, -0.1 percentage points; 95% confidence interval, -1.1 to 0.8; P = 0.71). There were also no significant differences in the secondary outcomes, including rates of return of spontaneous circulation on arrival at the emergency department, survival to hospital admission, and survival to hospital discharge. Use of the ITD did not significantly improve survival with satisfactory function among patients with out-of-hospital cardiac arrest receiving standard CPR. (N Engl J Med 2011;365:798-806.)

And;

The overall number and proportion of patients who survived to hospital discharge with a modified Rankin score of 3 was 260/4345 (6.0%) with a sham ITD and 254/4373 (5.8%) with an active ITD, $p=0.61$. There were no statistically significant differences in pre-specified subgroup analyses or safety measures... In this large effectiveness trial, manual chest compressions and an active ITD did not significantly improve functional survival from cardiac arrest compared with a sham ITD. (Circulation; 122:HT1)

As discussed below, the sponsor halted enrollment in an arm of the ResQ Trial study which evaluated isolated use of the ITD 16.0 with standard CPR. This arm of the IDE trial was similar to the ITD-arm of the ROC PRIMED Study. Data from this truncated arm of the ResQ Trial are presented below, and FDA also believes that the issues and results from ROC PRIMED may be relevant to the assessment of safety and effectiveness for the ResQCPR™ System.

ResQPOD ITD (inspiratory threshold of -21 cmH₂O – *not used in the ResQ Trial*)

There were four European clinical trials that evaluated the System (ACD and ITD) clinically, though the ITD used in each had an inspiratory threshold of -21 cm H₂O (whereas the ITD used in the ResQ Trial had an inspiratory threshold of -16mmH₂O):

- 21 randomized patients (excluded VF arrest patients); “focused on the acute hemodynamic effects of this valve during the performance of ACD CPR.”
- 210 randomized patients; “The primary study end point was 1-hour survival after hospital admission in witnessed cardiac arrest... The study was powered only to detect a difference in 1-hour survival rates.”
- 400 randomized patients (ACD + ITD vs. ACD + sham); “The primary endpoint of this study was 24 h survival...”
- 13 patients, each treated sequentially with ITD and sham; “The main end point of the present study was the evaluation of the maximum effect of an active ITD on airway pressures during the decompression phase of ACD CPR.”

ResQPOD Circulatory Enhancer (*not used in the ResQ Trial*)

The ResQPOD® Circulatory Enhancer (marketed in the US) includes a safety check valve that allows inspiration at -10cm H₂O, and has an indication that includes spontaneously breathing patients and those receiving assisted ventilation (cleared on June 11, 2003 under K022906):

“The ResQPOD® Circulatory Enhancer is indicated for home and hospital use, for the temporary increase in blood circulation as prescribed by a physician or licensed

practitioner.”

The indication was modified on November 20, 2003 (K033401) to state:

“The ResQPOD® Circulatory Enhancer is indicated for home, hospital, clinic, and emergency care use, for the temporary increase in blood circulation as directed by a physician or licensed practitioner.”

ResQPump® (used in the ResQTrial)

The ResQPump® was originally designed and marketed (outside the US) by Ambu International, under the name CardioPump. The CardioPump was presented to a US FDA Advisory Panel in 1998 (under PMA P970041) and a final recommendation for Not Approvable was reached (both by the Panel, as well as FDA) due to questions about both safety and effectiveness based on the data presented.

ASCI purchased the CardioPump from Ambu International in 2007, and obtained CE marking on December 17, 2008 with the following indications:

“The CardioPump is indicated for use in the treatment of adult patients with out-of-hospital cardiac arrest (absence of effective pulse and respiration) to improve the overall efficiency of CPR and the chances for short and long term survival.”

Neither component of the System utilized in P110024 (i.e., the ACD or the ITD) has been approved for clinical use in cardiac arrest in the United States. The ACD failed in 1998 to gain PMA approval for isolated use in cardiac arrest. A cleared version of the ITD (with an inspiratory threshold of -10 cm H₂O) is available in the United States, intended for spontaneously breathing patients (and thus not indicated for cardiac arrest). G050062 was to demonstrate the synergistic performance of the ACD and ITD devices when used together on cardiac arrest victims.

4.2 PMA Regulatory History

Advanced Circulatory Systems, Inc. (ASCI) applied for a pivotal study of the ResQCPR™ System under Investigational Device Exemption (IDE) application G050062, as a prospective, randomized, multi-center trial performed to evaluate the safety and effectiveness of the use of the ResQCPR™ System in patients with non-traumatic, out-of-hospital cardiac arrest. The application (G050062) was conditionally approved on April 21, 2005 for 350 training/run-in patients. The 3-arm Pivotal study was approved on October 27, 2005, with enrollment spanning from March 2006 to July 2009.

The original objective of the trial was to evaluate the impact of ACD- ITD on human survival and neurological outcome following cardiac arrest in a 3-arm study. The main hypothesis is that use of ACD-ITD will result in a statistically significant increase in survival to hospital discharge with a good neurologic outcome (modified Rankin Score [mRS]≤3) in adults after cardiac arrest when compared with s-CPR alone. It is further hypothesized that if use of ACD-ITD is found to significantly increase these survival rates, then use of the ITD with s-CPR will significantly increase survival rates as well, but to

a lesser degree, when compared with s-CPR alone in patients after cardiac arrest.

In 2007 the sponsor modified the trial to a two-armed study, where the objective was narrowed to compare the safety and effectiveness of s-CPR to ACD-ITD in subjects with out-of-hospital cardiac arrest. The main hypothesis is that use of ACD-ITD will result in a statistically significant increase in survival to hospital discharge with a good neurologic outcome ($mRS \leq 3$) in adults after cardiac arrest when compared with s-CPR alone.

Significant IDE supplements included:

- G050062/S012 [dated March 19, 2007] - ACSI requested the addition of a 6th study region/site (approved April 18, 2007);
- G050062/S016 [dated June 28, 2007] - ACSI proposed an adaptive design to adjust the sample size at the interim look with the inverse normal method (approved July 24, 2007).
- G050062/S018 [dated October 17, 2007] – ACSI requested to drop the s-ITD arm, with the study continuing as a 2-arm study, i.e., ACD-ITD vs. s-CPR (approved on November 14, 2007);
- G050062/S024 [dated November 24, 2008] - Following the pre-specified interim analysis (scheduled for 50% enrollment), ACSI requested an increase in their study size from 700 evaluable patients/arm to 1348 evaluable patients/arm, and also requested the addition of a 7th region/site (conditionally approved December 10, 2008);
- G050062/S030 [dated July 29, 2009] - ACSI indicated that enrollment into the ResQTrial would be suspended pending a resolution to funding issues;
- G050062/S031 [dated April 20, 2010] - study enrollment was officially terminated due to lack of funding. All sites were notified of enrollment termination on April 6, 2010.

At the time of enrollment suspension, only 1655 of the planned-for 2696 evaluable pivotal patients were enrolled in the 2-arm ResQTrial. For reasons discussed below, FDA is concerned about the validity of the sponsor's statistical inferences, when considered in the context of unplanned interim analyses in addition to other trial conduct issues discussed below.

In May 2010, the sponsor apprised FDA of its plans to submit a PMA with an enrollment equal to 61% of the approved increased study sample size enrollment, if, following the one year follow ups were completed "...the results are favorable to the investigational devices....". In October, 2010, the sponsor presented initial trial results to FDA, and PMA (P110024 - dated June 10, 2011) was filed on June 15, 2011. There have been 10 major Amendments to P110024.

5 IDE CLINICAL STUDY DESCRIPTION

5.1 Study Overview

IDE G050062 (the ResQTrial) was a prospective, randomized, multi-center trial initially intended to evaluate the safety and effectiveness of the ResQCPR™ System, as well as to assess the relative contributions of the System's two components (ACD and ITD) to the overall safety and effectiveness profile. Patients were randomized (under 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research) to receive standard CPR (s-CPR), CPR with both devices (ACD-ITD), or CPR with the ITD alone (s-ITD).

The National Institutes of Health (NIH) was a major funding source for the ResQTrial, and in 2008 the sponsor became aware that NIH funding would potentially cease in the latter part of 2009. In July 2009, following a DSMB meeting where concerns were raised regarding the availability of funds, new subject enrollment was suspended by the sponsor until continued future funding could be secured. In April, 2010, NIH denied any further funding of the trial, and the sponsor allocated its remaining funds to the completion of 1-year follow-up of the patients already enrolled.

Study Design

Sample size

The study included a run-in phase and a main pivotal phase. In the run-in phase, subjects were randomized and the data were to be analyzed separately from the pivotal phase. As mentioned above, the pivotal phase was originally designed as a 3-arm study to evaluate clinical outcomes in out-of-hospital cardiac arrest victims (i.e., hospital survival with good neurological outcome – defined as mRS \leq 3). Comparisons (superiority) were to be made between standard CPR (s-CPR) [Group 1], active compression/decompression (ACD) CPR + ITD (ACD-ITD) [Group 2], and impedance threshold device (ITD)+s-CPR (s-ITD) [Group 3].

Interim analyses were planned when 50% of the subjects had been enrolled in the s-CPR and ACD-ITD groups, and again when 50% of the subjects had been enrolled in the s-ITD group.

In the original protocol (dated 9/12/2005), an initial maximum sample size of 2100 evaluable patients (700 patients per arm who met final inclusion criteria) were planned to be randomized to the three treatment groups. Enrollment rates, however, did not meet trial design expectations, and enrollment in the CPR with ITD arm of the trial was abandoned in 2007, in an effort to enrich enrollment for what was perceived as the principal purpose of the study (namely, evaluation of the ResQCPR™ System as a whole (ACD in conjunction with ITD)).

The pre-specified interim look by the DSMB in 2008 (with data on approximately 52% of the total planned study population) concluded that “...an additional 985 patients per treatment group would be required, for an approximate total enrollment of 363 (current)

+ 985 (additional) = 1,348 patients per group.”

The original protocol contained the following information related to the sample size:

“Because the study contains a provision for interim analyses at the midpoints of enrollment in the three study arms, the realized sample size may also be lower than projections due to early stopping if statistical significance is achieved. Assumptions regarding hospital discharge rates, adverse events rates and percentages of evaluable subjects among enrollees used in the estimating study sample size requirements will be reassessed and validated after the run-in phase.”

It is noteworthy that an increase in sample size based on the pivotal trial interim look was not clearly stated in the original protocol. The sample size re-estimation plan (G050062/S016) was submitted in 2007, 1 ½ years after enrollment in the pivotal phase had begun (March, 2006), and one year prior to the midpoint interim analysis in September 2008. FDA approved the sample size increase in July 2009.

FDA approved this change in July 2007. The initial intention of the interim look, in the original study protocol was to stop the trial for early success. In the revised SAP, approved by FDA, the interim analysis was modified to permit recalculation of the sample size. However, because the sponsor was effectively unblinded from 10/20/06 onward (see below), FDA would consider this sample size re-estimation plan to have been a post-hoc proposal. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

History of proposed major study design modifications

The trial’s independent Data and Safety Monitoring Board (DSMB) met regularly throughout the study (10/27/06, 9/27/07, 9/5/08, and 7/9/09) and reviewed group specific data. The DSMB serially generated detailed reports about study progress which were communicated to the sponsor. Data tables generated for the DSMB reports as well as correspondence between the DSMB and the sponsor were provided to FDA in the required IDE Annual Reports. An example of the type of data presentations available to the sponsor is shown below (DSMB meeting 9/05/2008; G050062/S27 Annual Report dated 4/21/09). It is apparent to FDA that explicit unblinding of the group-specific interim primary endpoint results was readily obtainable by the sponsor since 2006. When FDA discovered the potential for complete unblinding, the agency brought this issue to the company’s attention. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

Group-specific Primary Endpoint Data

Table 18: **Survival to Hospital Discharge**

| Group | Group A | Count | Was the patient discharged from the hospital alive? | | | Total |
|---------|----------------|-------|---|------|---------|-------|
| | | | Yes | No | Unknown | |
| Group A | Count | 51 | 162 | 1 | 214 | |
| | % within Group | 23.8% | 75.7% | .5% | 100.0% | |
| Group B | Count | 43 | 177 | 3 | 223 | |
| | % within Group | 19.3% | 79.4% | 1.3% | 100.0% | |
| Total | Count | 94 | 339 | 4 | 437 | |
| | % within Group | 21.5% | 77.6% | .9% | 100.0% | |

Note: Total number of 437 represents those transported to hospital and not still hospitalized

Table 23: **Success/Failure on Modified Rankin Score at Discharge**

| Group | Group A | Count | Modified Rankin Score Group | | Total |
|---------|----------------|-------|-----------------------------|-----------|-------|
| | | | Score ≤ 3 | Score > 3 | |
| Group A | Count | 30 | 17 | 47 | |
| | % within Group | 63.8% | 36.2% | 100.0% | |
| Group B | Count | 20 | 13 | 33 | |
| | % within Group | 60.6% | 39.4% | 100.0% | |
| Total | Count | 50 | 30 | 80 | |
| | % within Group | 62.5% | 37.5% | 100.0% | |

Potential Complete Unblinding of Groups

Table 14: **Return of Pulse**

| Group | Group A | Count | Return of Pulse | | Total |
|---------|----------------|-------|-----------------|--------|-------|
| | | | No | Yes | |
| Group A | Count | 217 | 147 | 364 | |
| | % within Group | 59.6% | 40.4% | 100.0% | |
| Group B | Count | 205 | 157 | 362 | |
| | % within Group | 56.6% | 43.4% | 100.0% | |
| Total | Count | 422 | 304 | 726 | |
| | % within Group | 58.1% | 41.9% | 100.0% | |

Table 1: **CPR Duration (min) if no ROSC Achieved**

| Site | CPR Method | CPR Method | | Total |
|-------|------------|------------|-------------|-------|
| | | S-CPR | ACD-CPR+HTD | |
| 1 | Mean | 31.7 | 35.3 | 33.6 |
| | Median | 32.0 | 34.0 | 32.5 |
| | Minimum | 15 | 30 | 15 |
| | Maximum | 63 | 59 | 63 |
| 6 | Mean | 15.7 | 38.2 | 32 |
| | Median | 30.5 | 40.0 | 40.0 |
| | Minimum | 24 | 28 | 24 |
| | Maximum | 46 | 47 | 47 |
| Total | Mean | 31.4 | 32.1 | 31.8 |
| | Median | 31.0 | 31.0 | 31.0 |
| | Minimum | 6 | 9 | 6 |
| | Maximum | 63 | 59 | 63 |
| Total | Ni | 205 | 217 | 422 |

With this potential for unblinding in mind, FDA points out the timeline for the following study design modifications proposed by the sponsor:

- G050062/S011 (following DSMB meeting 10/20/06) - change randomization ratio of the 3-armed trial from 2:2:1 to 7:7:1. The request was disapproved by FDA due to concerns of its leading to inappropriate group sizes by study conclusion.
- G050062/S016 (following DSMB meeting 10/20/06) - an adaptive design to adjust the sample size at the pre-specified interim look (at 50% enrollment) with the inverse normal method.

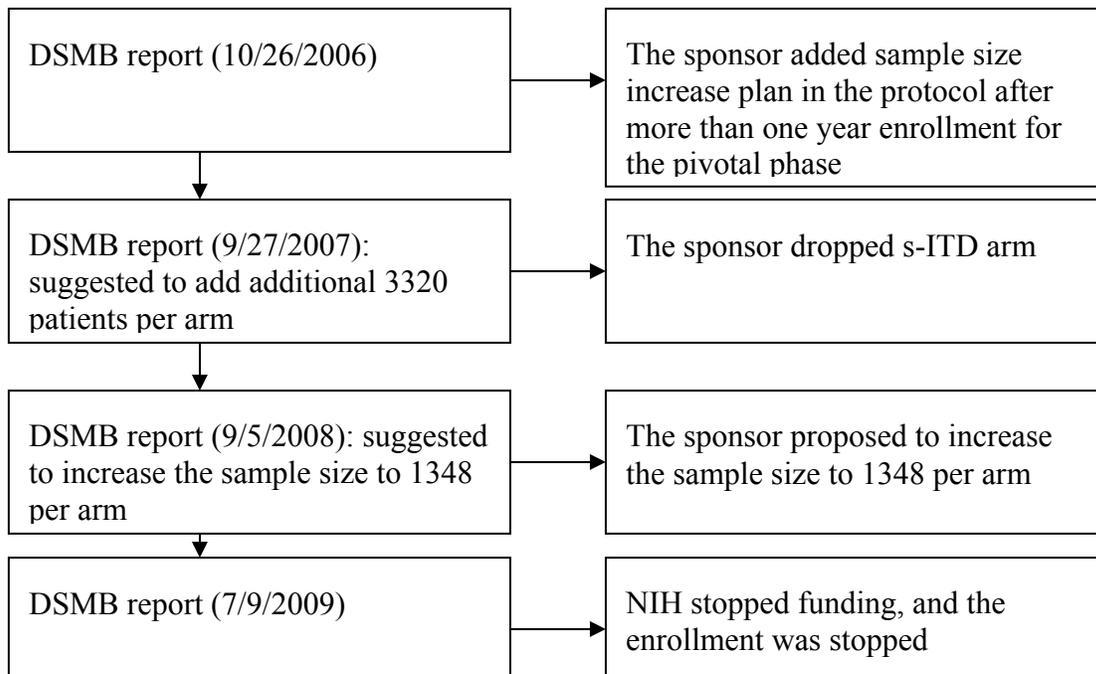
The request was approved by FDA in July 2007. It is possible that this trial modification may have been considered by the sponsor in the setting of an unplanned effectively unblinded interim analysis involving group-specific data. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

- G050062/S018 (following the 9/27/2007 DSMB meeting) - abandon the s-ITD arm of the study. The sponsor explained that “since the interim analysis has not yet been performed and study results by treatment group remains blinded, no alpha amount has yet been spent. This change will affect the size of the detectable treatment effect between Groups 1 and 2 for a given study enrollment, but materially affects no other aspects of the existing data analysis plans.”

FDA approved the request to drop the s-ITD arm in March 2008. FDA, in retrospect, disagrees with the sponsor’s statement made above.

The sponsor had described the ACD and the ITD as working “synergistically...[resulting]in a unique mechanical and physiological advantage over s-CPR”; FDA’s opinion is that the available s-ITD data can substantively inform the overall characterization of the ResQCPR™ System as a whole. These data are discussed later. Similarly, the ResQTrial’s evaluation of the s-ITD arm was very similar to the ITD’s evaluation in ROC PRIMED. FDA believes that the data from the ROC PRIMED Study provides relevant, information regarding the ResQCPR™ System.

- G050062/S024 (following the 9/05/2008 DSMB meeting and pre-specified interim look) - to increase the sample size to 1348 pivotal patients/group (2696 evaluable pivotal patients).
- G050062/S30 (following the 7/9/2009 DSMB meeting) - patient enrollment suspended at all sites, effective July 29, 2009, secondary to funding issues (concerns expressed by the DSMB). On 4/5/10 NIH indicated there would be no NHLBI funding of the ResQTrial. On 4/6/2010, additional patient enrollment was terminated.



FDA is concerned that effective blinding for the ResQ Trial was, from a statistical standpoint, broken at the time of each DSMB analysis (10/27/06, 9/27/07, 9/5/08, and 7/9/09), since discrete information on treatment group results—even though *encrypted*—were sent to the sponsor. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

FDA cannot quantify the level of operational bias or Type 1 error rate inflation, if any, that may have been introduced into the study by the effective unblinding during these unplanned interim analyses, but believes there may be resulting limitations to the clinical conclusions that can be drawn from the study.

Inclusion/Exclusion Criteria

The specific inclusion and exclusion criteria used to determine whether or not any given patient would be initially enrolled into one of the two study arms is described below. Initial criteria applied to screened patients defined the Intention-to-Treat (ITT) analysis population. Final criteria were applied to the provisionally enrolled ITT patients, yielding a modified Intention-to-Treat population (mITT). All cases that failed to transition from ITT to mITT were to be adjudicated by the blinded, independent Clinical Events Committee (CEC), whose charter was formulated in March, 2009.

Initial Inclusion Criteria

1. Adult subjects initially presumed or known to be 18 years of age or older
2. Subjects who present with presumed non-traumatic, out-of-hospital cardiac arrest and who are candidates for resuscitation attempts.

Initial Exclusion Criteria

1. Subjects initially presumed or known to be < 18 years of age
2. Subjects with obvious or likely traumatic injuries causing cardiac arrest
3. Subjects with pre-existing DNR orders
4. Subjects with signs of obvious clinical death or conditions that preclude the use of CPR
5. Subjects whose family or legal guardians request that the subject not be entered in the study at the time of arrest
6. Subjects experiencing in-hospital cardiac arrest
7. Recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known)

Final Inclusion Criteria

1. Adult subjects initially presumed or known to be 18 years of age or older
2. Subjects who present with out-of-hospital cardiac arrest from presumed cardiac etiology or medication/drug overdose and who receive CPR by EMS personnel for at least one minute
3. Subjects whose airways are managed with a cuffed ET tube, Combitube or laryngeal mask airway or facemask.

Final Exclusion Criteria

1. Adult subjects presumed or known to be < 18 years of age
2. Subjects with known or likely traumatic injuries causing cardiac arrest or cardiac arrest of presumed non-cardiac origin (exception: medication/drug overdose)
3. Subjects with pre-existing DNR orders
4. Subjects with signs of obvious clinical death or conditions that preclude the use of CPR
5. Family or legal representative request that the subject not be entered into the study
6. Subjects experiencing in-hospital cardiac arrest
7. Subjects with a recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known)

8. Subjects who received less than one minute of CPR by EMS personnel
9. Subjects with a complete airway obstruction that cannot be cleared or in whom attempts at advanced airway management are unsuccessful
10. Subjects intubated with a leaky or uncuffed advanced airway device or presence of stomas, tracheotomies or tracheostomies
11. Subjects who re-arrest and are encountered by EMS within 365 days of the index cardiac arrest

ACSI excluded 163 patients from the mITT analysis based on cardiac arrest of presumed medication/drug overdose in conflict with the approved protocol (G050062/S9, dated April 20, 2006). Additionally, 28 cases were provided to the CEC for late adjudication and removal from the mITT population/analysis.

Primary Endpoint

The primary endpoint was defined as survival to hospital discharge with a good neurologic outcome in subjects experiencing out-of-hospital cardiac arrest from presumed cardiac etiology. A good neurologic outcome was defined as a Rankin Score of 3 or less using the Modified Rankin Scale (mRS):

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

The protocol mandated that mRS data be obtained from a structured interview conducted by trained individuals. As discussed below, mRS data on some patients were derived and/or changed on the basis of information obtained outside of a discrete patient interview, often at a time remote from the arrest event. FDA is concerned that this data collection process may affect the strength of effectiveness inferences that are based upon the primary endpoint.

Secondary Endpoints

Safety

The secondary safety endpoint was a composite of major adverse events (MAE) including:

- Death
- Cerebral bleeding
- Bleeding requiring transfusion or surgical intervention
- Seizures
- Re-arrest
- Pulmonary Edema
- Serious rib fractures/sternal fractures
- All internal thoracic and abdominal injuries
- All device malfunctions, defects, failures*

**Final analyses of the secondary safety endpoint did not include device malfunction, etc., since the control arm would not have this event.*

Effectiveness

The secondary effectiveness endpoint was defined as long-term neurologic function assessed using the Cognitive Abilities Screening Instrument (CASI) at 90 days and 1 year post-cardiac arrest in surviving subjects.

Selected Additional Secondary Endpoints:

Derived from Utstein Consensus Conference guidelines

- The Glasgow-Pittsburgh Outcome Categorization of Brain Injury (discharge, 30, 90, 365 days)
 - Cerebral Performance Categories (CPC)
 - Overall Performance Categories.(OPC)
- Return of spontaneous circulation (ROSC)
- Survival (1hour, hospital admission,24 hours, 30, 60, 365 days)

Clinical Study Centers

Five sites (defined as regions for the purpose of community consultation and public notification – required under §50.24) were originally planned for the ResQ Trial, but two additional sites/communities were added by the end of the study. The 6th site was approved to be added in April 2007. The 7th site was added in March 2009. These 7 sites included a total of approximately 26 IRBs and 40 enrolling centers.

5.2 Statistical Analysis Plan

The following provides an overview of the statistical analysis plan described in the protocol, including a planned interim look and stopping rules.

Analysis Populations

Screening population: all patients with presumed cardiac arrest occurring within the primary response area of the EMS system.

Because of the nature of receiving treatment under a waiver of informed consent (§50.24), mITT was proposed as the primary analysis population:

Intention-to-treat (ITT): all randomized patients. This was specified as the supplementary analysis set.

Modified intention-to-treat (mITT): the randomized patients who met the final inclusion and exclusion criteria. This was specified as the primary analysis set because subjects might receive the randomized treatment under waiver of informed consent provisions in this study and later be found not to meet enrollment requirements.

Beginning shortly after its initial review of the PMA dataset, FDA informed the sponsor that adjunctive analyses would be important for the Agency's assessment of effectiveness to assess the robustness of the key results. In particular, FDA indicated that appropriate assessment of the primary endpoint result's robustness would be facilitated by a "per-protocol" and *post hoc* "as-treated" analyses. These analyses are presented below.

Hypotheses

Primary endpoint (Superiority)

Survival to hospital discharge with good neurologic outcome ($mRS \leq 3$) was specified to test for device superiority for s-CPR vs. ACD-ITD and s-CPR vs. s-ITD. Note that the powered analysis for s-CPR vs. s-ITD was subsequently abandoned by the sponsor due to dropping the s-ITD arm from the study; a non-hypothesis-driven analysis was performed instead. See Appendix 1 for hypothesis test.

Secondary safety endpoint (Non-inferiority)

The secondary safety endpoint evaluated major adverse event rate (MAE) and evaluated non-inferiority with a non-inferiority margin of 5% for s-CPR vs. ACD-ITD and s-CPR vs. s-ITD (this analysis was subsequently abandoned due to dropping the s-ITD arm from the study). See Appendix 1 for hypothesis test.

Secondary effectiveness endpoints (Superiority)

The secondary effectiveness endpoint evaluated neurologic function, i.e., CASI score, at 90

days and 1 year for device superiority for s-CPR vs. ACD-ITD and s-CPR vs. s-ITD (this analysis was subsequently abandoned due to dropping the s-ITD arm from the study). See Appendix 1 for hypothesis test.

Sample Size Adjustment

Run-in Phase

For the run-in phase, in the original protocol, approximately 350 subjects were to be enrolled and randomized to the s-CPR, s-ITD and ACD-ITD arms (unspecified randomization ratio). After ACSI abandoned the s-ITD arm of the study, and added two additional sites the updated version of the protocol allowed for approximately 400 subjects to be enrolled and randomized (unspecified ratio) to the s-CPR and ACD-ITD arms. The run-in phase screened a total of 746 subjects, 334 of which met the initial selection criteria (ITT) and were randomized to S-CPR, ACD-ITD, and S-CPR+ITD:

Pivotal phase

The sample size is driven by the primary hypothesis test. In the original protocol (dated 9/12/05), 700 evaluable subjects in each of the three treatment arms would have 80% power to detect a clinical difference of 4.9% if the s-CPR survival rate was 6%. In the new protocol (dated 10/15/07 - after abandoning the s-ITD arm), the initial sample size for the s-CPR and ACD-ITD arms was not changed, i.e., ACSI anticipated that up to 2100 patients would need to be enrolled to obtain 1400 evaluable patients who satisfied the final inclusion criteria. After the planned interim analysis (52% of enrollment [~1452], the data were locked in February 2008, and the DSMB meeting was held on September 5, 2008), however, the number of evaluable patients was increased from 700 per group to 1348 per group (2696 total). (Additional sample size discussion is found in Appendix 2.)

Interim Analysis

Interim analyses were planned at 50% enrollment of s-CPR and ACD-ITD arms, then again at 50% enrollment into the s-ITD arm. The test significance levels of 0.005 and 0.022 were specified for the interim analysis and for the final analysis (two-sided for the primary endpoint and one-sided for the secondary safety endpoint). The primary endpoint and the secondary safety endpoint were planned to be analyzed at the interim analysis, but the secondary effectiveness endpoints CASI scores at 90 days and 1-year would only be evaluated at the completion of the study.

In retrospect, the interim analysis plan was not optimally developed in the original protocol. For example:

- 1) The detailed enrollment strategy and analysis plan were not specified for the interim look and the final analysis.
- 2) The strategy to control the overall type I error was not sufficiently specified.
- 3) The plan did not clearly specify who should be masked to the interim analysis results.

In the updated version of the protocol and SAP, the s-ITD arm was dropped from the study, and the significance level was changed to 0.003 at the interim look (50% of the data) and 0.049 at the final analysis after dropping the s-ITD arm. The significance level was two-sided for the primary endpoint and one-sided for the secondary safety endpoint.

The decision to drop the s-ITD arm (requested in G050062/S018, 10/17/07) was made soon after an interim analysis report (DSMB report dated 9/27/07) was presented to the sponsor.

A sample size increase plan was also added in the revised SAP (February 25, 2008). The inverse normal method was planned.

Multiple Tests Plan

In both the initial (9/12/05) and the updated (10/15/07) protocols, the following “hierarchical closed test procedure” was specified for the primary and secondary effectiveness endpoints:

- 1) If statistical significance was achieved for the primary endpoint, an additional overall significance level of 0.05 would be applied to Neurologic function at 90 days.
- 2) If significant at 90 days, a significance level of 0.05 would be applied to Neurologic function at 1 year.

The secondary safety endpoint was not considered in the multiple tests plan. Thus the study overall type I error was not controlled at 0.05.

In the updated statistical analysis plan (SAP) (February 25, 2008), the following “hierarchical closed test procedure” was specified:

- 1) If statistical significance was achieved for the primary endpoint at the conclusion of the study, then evaluate the secondary safety endpoint at 0.049.
- 2) If statistical significance was achieved on both the primary endpoint and the secondary safety endpoint, then an additional overall significance level of 0.05 would be applied to neurology function at 90 days.
- 3) If significant at 90 days, a significance level of 0.05 would be applied to neurologic function at 1 year.

5.3 Informed Consent

The ResQTrial was conducted in accordance with 21CFR 50.24 (§50.24): *Exception from informed consent requirements for emergency research*. The study and patient population met all the requirements as outlined in the regulation, most importantly;

- the subjects are in a life threatening situation,
- obtaining informed consent is not feasible due to the fact that the intervention needs to be applied right away, and
- participation in the research holds out the prospect of direct benefit to the subjects.

Community Consultation and Public Notification

§50.24 requires the study sponsor to perform Community Consultation (CC) and Public Notification in advance of the study. The methods to be used are not specifically defined in the regulations, but Advanced Circulatory Systems, Inc. appeared to do a comprehensive job attempting to reach as much of the community as possible. In summary, ACSI included the following methods to reach and inform the community of the proposed study (including the risks and benefits):

- meetings,
- television,
- radio,
- newspaper/printed notice,
- direct mailings, and
- websites

The sponsor was required to provide certification of completion of community consultation/public notification and evidence of IRB approval prior to the site initiating enrollment into the study. These materials were presented to FDA for review in the IDE, and are also presented in this PMA.

Some important items to note for a study performed under 21 CFR 50.24:

- All patients who meet the inclusion criteria are enrolled into the study;
- If a family member or legally authorized representative (LAR) is present before the study devices are applied, they have the right to request that the study devices not be used;
- The enrolled patients (or their LAR or family member) are to be approached within a feasible/reasonable timeframe (ideally within 2-4 days of hospital admission), will be advised of the subject's enrollment into the study, and will be requested for consent to continue in the study;
- The patient, family member, or LAR will be offered the option to opt out of further participation when initially approached (verbal or written notification is acceptable);
- Data from a patient who has opted out of further participation can only be included in the study up to the point of withdrawal;
- All data, up to the point of withdrawal (if a patient declines further participation) are to remain in the study.

Due to the emergency nature of cardiac arrest, treatment must be initiated immediately. As such, all subjects who met the initial selection criteria (as evaluated by the EMS) were enrolled in the study (ITT patient population). If a subject's legal representative/family member was present, they had the right to request that the study devices not be used – the sponsor states that this happened in 2 cases (0.1%).

For subjects who survived to hospital admission, the subject (if able), family member, or legally authorized representative were approached for consent. Although ideally this process should begin within the first three days of the subject's hospital stay, the exact time for the ResQ Trial was determined in part by the condition and the emotional state of the family members. As such, the average number of days from cardiac arrest to consent in the ResQ Trial was 15.7 + 38.0 [Range: 0 – 303 days]. The mean number of days from cardiac arrest to completion of notification was 38 days. For subjects who did not survive to hospital admission, the family was notified via letter or telephone conversation.

The ACSI consent process included 1) notification of enrollment into the study, 2) request for permission to allow review of the subject's hospital medical record, and 3) a request for the subject's continued participation in the study for up to one year. Written consent was obtained when at all possible, and 71% of patients who were admitted to the hospital provided consent; 18% declined further participation (54 s-CPR subjects, 36 ACD-ITD subjects); and consent/declination of consent was unable to be obtained from 10% of patients. It should also be noted that more control arm patients declined consent (54) than test arm patients (36).

5.4 Study Conduct

Run-in Phase

The sponsor states that concerted training of the involved emergency medical system (EMS) personnel is essential for appropriate use of the System, and it accordingly planned for a large run-in phase for the trial (400 patients). The length of the run-in phase was based on the predicted incidence of EMS responses to cardiac arrest (“an average of <1 cardiac arrest per day per EMS rig”). For each site, the sponsor anticipated that 6 months would be required for proper implementation of the technology after an initial 3 month training phase. The run-in phase followed the protocol and monitoring policies. Pivotal enrollment at a site was not initiated until the sponsor had certified site competency with protocol execution with the following criteria:

- Based upon field spot checks by a member of the site's research team, EMS personnel appear to have mastered the s-CPR and ACD-CPR methods and are using the ITD correctly.
- Subjects were being enrolled with no (or minimal) randomization errors.
- Data collection processes were occurring smoothly.
- Subjects were being notified and consented as per study protocol.
- Adverse events were being captured, reported and handled per study protocol.

Table 12 Enrollment by Site/Run-in Phase, ITT¹ [N=746 with cardiac arrest, 334 provisionally enrolled]

| Site | Phase duration | Subjects who met INITIAL criteria (ITT) | | | Total provisionally enrolled | Subjects who met FINAL criteria (mITT) | | | Total subjects who met FINAL criteria | Total screened |
|--------------|----------------------|---|------------|------------|------------------------------|--|-----------|-----------|---------------------------------------|----------------|
| | | S-CPR+ITD | S-CPR | ACD+ITD | | S-CPR+ITD | S-CPR | ACD+ITD | | |
| 01 | 10/3/05 to 2/26/06 | 7 | 17 | 27 | 51 | 4 | 13 | 19 | 36 | 163 |
| 02 | 12/17/05 to 5/26/06 | 21 | 32 | 34 | 87 | 17 | 24 | 27 | 68 | 121 |
| 03 | 10/2/05 to 4/15/06 | 9 | 26 | 19 | 54 | 5 | 16 | 12 | 33 | 116 |
| 04 | 11/13/05 to 4/1/06 | 17 | 27 | 25 | 69 | 15 | 25 | 20 | 60 | 162 |
| 05 | 10/23/05 to 2/25/06 | 4 | 5 | 4 | 13 | 4 | 5 | 1 | 10 | 42 |
| 06 | 11/12/07 to 12/17/07 | 8 | 15 | 11 | 34 | 5 | 9 | 10 | 24 | 84 |
| 07 | 3/18/09 to 4/9/09 | NA | 12 | 14 | 26 | NA | 7 | 9 | 16 | 58 |
| TOTAL | | 66 | 134 | 134 | 334 | 50 | 99 | 98 | 247 | 746 |

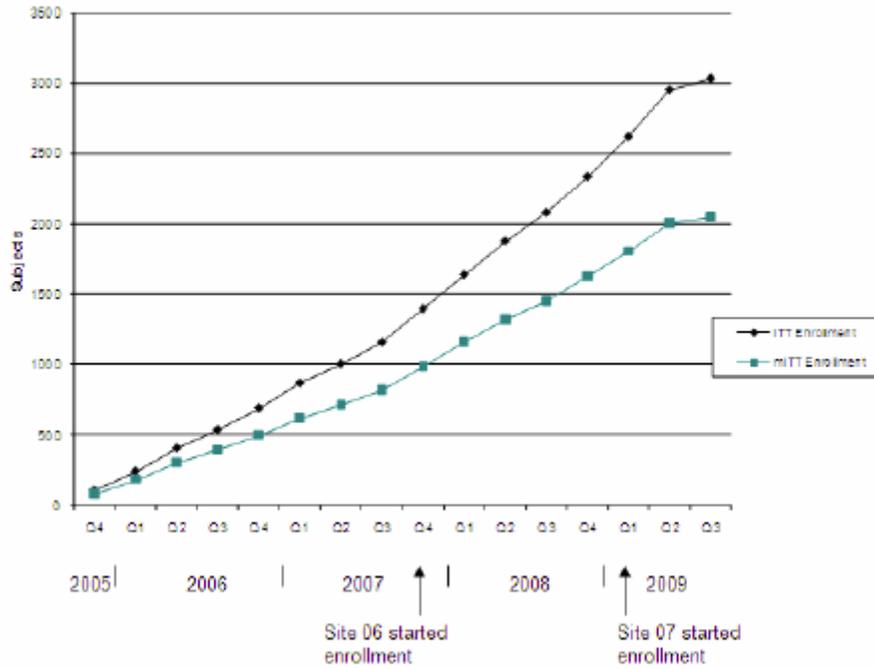
(Source: Appendix 13c, Listing 121; Listing 122; Listing 121.5- Reasons for screening failure)

¹ “Phase duration” includes dates of first and last enrollment. Subjects who met initial selection criteria received the randomized CPR treatment (e.g., provisionally enrolled). New enrollment in the S-CPR+ITD arm was discontinued, and the last run-in phase subject was enrolled in this arm on December 16, 2007. “Total screened” includes all subjects in whom there was EMS dispatch for cardiac arrest; and thus includes subjects who did not meet the initial selection criteria, and who met the initial criteria and were provisionally enrolled.

The two sites added later in the trial (Sites 06 and 07) were deemed certified by the sponsor after one month or less; the run-in phase for Sites 01-05, by contrast, required approximately four or five months each. The sponsor explained this discrepancy by citing its larger and more experienced clinical staff which allowed for more efficient technical and procedural training in the latter part of the trial.

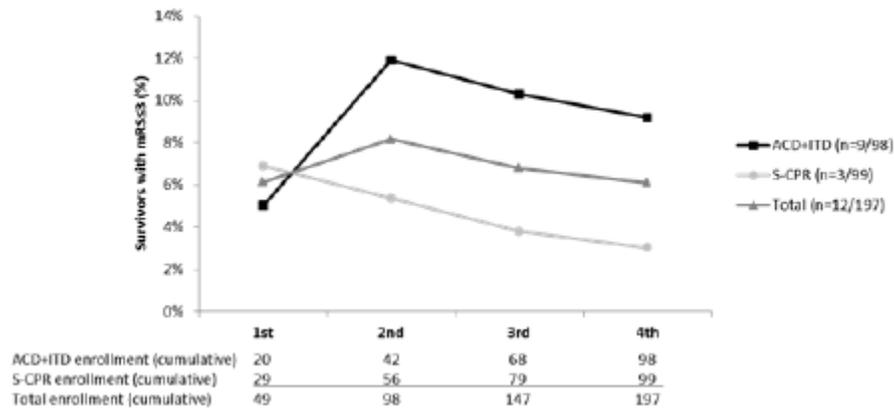
The rate of trial enrollment in this multi-year trial increased after the certification of Site 06:

Figure 5 Cumulative Enrollment, all subjects (combined run-in and pivotal phases)

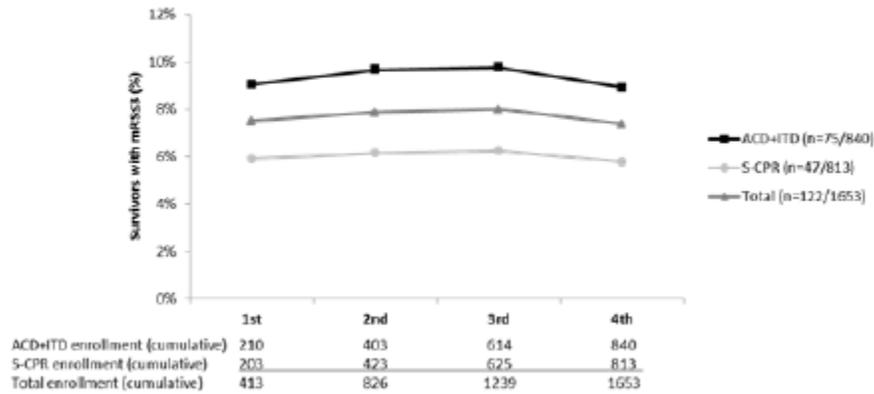


For both s-CPR and ACD-ITD patients, later trial enrollment was associated with a decrease in successful attainment of the primary endpoint (i.e., survival to hospital discharge with good neurological function). The change was particularly evident for the run-in phase’s fourth quartile (4/21/2006-4/8/2009), the period spanning the introduction of Sites 06 and 07.

B. Run-in Phase:



A. Pivotal Phase:



Sites 06 and 07 also accrued the highest rates of major protocol violations during the pivotal phase of the trial.

Our assimilation of enrollment rates, major protocol violations, and primary endpoint outcomes data raises the possibility that factors related to sites' execution of the protocol over time may have had an impact on the global safety and effectiveness results.

Pivotal Phase

Unless specifically noted otherwise, the discussion for the remainder of this review concerns data from the pivotal portion of the ResQ Trial.

Patient Accountability

A total of 5783 patients were screened (as cardiac arrest victims) in the field for enrollment into the 3-armed study at 7 sites between March, 2006, and July, 2009. 2698 patients were provisionally enrolled on the basis of the initial inclusion/exclusion criteria (ITT cohort); 228 of this ITT cohort were randomized to the eventually suspended s-ITD arm, thus leading to a 2-armed ITT cohort of 2470 (1269 (51%) ACD-ITD and 1201 (49%) s-CPR). The final inclusion/exclusion criteria for the 2-armed ITT cohort yielded the mITT cohort of 1655 patients (842 ACD-ITD and 813 s-CPR). Thus 34% of the ITT treatment arm (i.e., ACD-ITD) and 32% of the ITT control arm (i.e., s-CPR) patients were excluded from the mITT analyses.

For the pivotal phase (two-armed trial), the top 3 enrolling sites (#2, 4, and 6) together enrolled 62% of the ITT patients (1524/2470) and 63% of the mITT population (1039/1655).

Table 13 Enrollment by Site, Pivotal Phase, ITT¹ [N= 5783 with cardiac arrest, 2698 provisionally enrolled]

| Site | Phase duration | Subjects who met INITIAL criteria (ITT) | | | Total provisionally enrolled | Subjects who met FINAL criteria (mITT) ² | | | Total subjects who met FINAL criteria | Total screened |
|--------------|---------------------|---|-------------|-------------|------------------------------|---|------------|------------|---------------------------------------|----------------|
| | | S-CPR+ITD | S-CPR | ACD+ITD | | S-CPR+ITD | S-CPR | ACD+ITD | | |
| 01 | 2/27/06 to 7/29/09 | 38 | 170 | 189 | 397 | 24 | 122 | 121 | 267 | 1054 |
| 02 | 5/27/06 to 7/28/09 | 62 | 246 | 286 | 594 | 43 | 155 | 169 | 367 | 1045 |
| 03 | 4/16/06 to 7/27/09 | 37 | 180 | 160 | 377 | 23 | 113 | 92 | 228 | 794 |
| 04 | 4/2/06 to 7/3/09 | 61 | 256 | 267 | 584 | 39 | 189 | 208 | 436 | 1243 |
| 05 | 2/26/06 to 7/20/09 | 13 | 59 | 47 | 119 | 10 | 46 | 40 | 96 | 309 |
| 06 | 12/18/07 to 7/29/09 | 17 | 222 | 247 | 486 | 11 | 149 | 169 | 329 | 1096 |
| 07 | 4/10/09 to 7/28/09 | NA | 68 | 73 | 141 | NA | 39 | 41 | 80 | 242 |
| TOTAL | | 228 | 1201 | 1269 | 2698 | 150 | 813 | 840 | 1803 | 5783 |

(Source: Appendix 13c, Listing 123; Listing 124; Listing 123.5- Reasons for Screening Failure)

¹ "Phase duration" includes dates of first and last enrollment. Subjects who met initial selection criteria received the randomized CPR treatment (e.g., provisionally enrolled). New enrollment in the S-CPR+ITD arm was discontinued, and the last pivotal phase subject was enrolled in this arm on May 11, 2008.

² "Total screened" includes all subjects in whom there was EMS dispatch for cardiac arrest; and thus includes subjects who did not meet the initial selection criteria, and who met the initial criteria and were provisionally enrolled.

Screening failures

Screening failures (in the field) of potential patients varied between 42% and 62% across the 7 sites. The reasons for screening failure, in aggregate, appear to have been well-balanced.

Adjudicated Enrollment

The CEC charter was explicit for the process by which an ITT patient could be excluded from the primary mITT population:

The committee will meet regularly to review individual cases proposed for exclusion from the study endpoint to ensure that the inclusion and exclusion criteria detailed in the protocol are being applied and followed appropriately. Using the a priori criteria defined in the protocol, the CEC will act as the final arbiter for these cases, and will determine the final disposition by majority vote.

Overall, 67% (1655/2470) of the patients provisionally enrolled into the 2-armed trial (ITT) were adjudicated as having also met the final inclusion/exclusion criteria (mITT). The sites' percentage of adjudication to mITT enrollment varied from 57% (Site 7) to 81% (Site 5).

For a given site the s-CPR and ACD-ITD mITT exclusion rates were similar, which suggests to FDA that the intra-site execution of the field protocol was similar for both arms of the study. The variability across sites in screening and final enrollment rates is clinically reasonable for a trial of this scope; however, FDA notes that the variability may also reflect some heterogeneity regarding sites' execution of the field (EMS) portion of the protocol.

Adjudicated reasons for excluding ITT patients from the mITT population are listed below. In aggregate, the presence of these exclusionary criteria appears to be clinically similar across the s-CPR and ACD-ITD arms.

Reason excluded from final data analysis * Group Crosstabulation

| | | | Group | | | Total |
|--|--|----------------|--------|-------------|-----------|-------|
| | | | S-CPR | ACD-CPR+ITD | S-CPR+ITD | |
| Reason excluded from final data analysis | Less than 18 years old | Count | 0 | 1 | 0 | 1 |
| | | % within Group | .0% | .2% | .0% | .1% |
| | Pre-existing DNR order | Count | 68 | 54 | 26 | 148 |
| | | % within Group | 17.5% | 12.6% | 33.3% | 16.5% |
| | Signs of obvious clinical death | Count | 23 | 22 | 3 | 48 |
| | | % within Group | 5.9% | 5.1% | 3.8% | 5.4% |
| | Recent sternotomy | Count | 3 | 3 | 0 | 6 |
| | | % within Group | .8% | .7% | .0% | .7% |
| | Prisoner (Site #1, #2, #5 and #6 Only) | Count | 1 | 1 | 0 | 2 |
| | | % within Group | 3% | .2% | .0% | .2% |
| | Presumed non-cardiac etiology | Count | 256 | 296 | 39 | 591 |
| | | % within Group | 66.0% | 69.0% | 50.0% | 66.0% |
| | Leaky or uncuffed advanced airway | Count | 12 | 21 | 1 | 34 |
| | | % within Group | 3.1% | 4.9% | 1.3% | 3.8% |
| | Unable to clear airway obstruction | Count | 17 | 18 | 4 | 39 |
| | | % within Group | 4.4% | 4.2% | 5.1% | 4.4% |
| Received < 1 minute of CPR | Count | 8 | 13 | 5 | 26 | |
| | % within Group | 2.1% | 3.0% | 6.4% | 2.9% | |
| Total | Count | 388 | 429 | 78 | 895 | |
| | % within Group | 100.0% | 100.0% | 100.0% | 100.0% | |

“Presumed non-cardiac etiology” accounted for the majority of randomized patients’ having been excluded from the mITT analysis population (69% (294/427) ACD-ITD; 66% (256/388) s-CPR) .

Non-cardiac etiology * Group Crosstabulation

| | | | Group | | | Total |
|----------------------|----------------------|----------------|--------|-------------|-----------|--------|
| | | | S-CPR | ACD-CPR+ITD | S-CPR+ITD | |
| Non-cardiac etiology | Other | Count | 85 | 78 | 4 | 167 |
| | | % within Group | 33.2% | 26.4% | 10.3% | 28.3% |
| | Trauma | Count | 3 | 10 | 2 | 15 |
| | | % within Group | 1.2% | 3.4% | 5.1% | 2.5% |
| | Drowning | Count | 4 | 4 | 2 | 10 |
| | | % within Group | 1.6% | 1.4% | 5.1% | 1.7% |
| Total | Smoke Inhalation | Count | 0 | 0 | 1 | 1 |
| | | % within Group | .0% | .0% | 2.6% | .2% |
| | CVA | Count | 11 | 8 | 3 | 22 |
| | | % within Group | 4.3% | 2.7% | 7.7% | 3.7% |
| | Drug Overdose | Count | 65 | 98 | 9 | 172 |
| | | % within Group | 25.4% | 33.1% | 23.1% | 29.1% |
| | Respiratory etiology | Count | 64 | 72 | 10 | 146 |
| | | % within Group | 25.0% | 24.3% | 25.6% | 24.7% |
| | Burns | Count | 0 | 1 | 0 | 1 |
| | | % within Group | .0% | .3% | .0% | .2% |
| | Metabolic imbalance | Count | 12 | 18 | 6 | 36 |
| | | % within Group | 4.7% | 6.1% | 15.4% | 6.1% |
| | Seizure | Count | 10 | 6 | 1 | 17 |
| | | % within Group | 3.9% | 2.0% | 2.6% | 2.9% |
| | Hypothermia | Count | 1 | 1 | 1 | 3 |
| | | % within Group | .4% | .3% | 2.6% | .5% |
| | Hyperthermia | Count | 1 | 0 | 0 | 1 |
| | | % within Group | .4% | .0% | .0% | .2% |
| | Total | Count | 256 | 296 | 39 | 591 |
| | | % within Group | 100.0% | 100.0% | 100.0% | 100.0% |

FDA reviewed line data of ITT patients excluded from the mITT cohort on the basis of non-cardiac etiology, and there appeared to be differences between the two arms in the sub-categorization of non-cardiac etiology. Proportionately more treatment-arm cardiac arrests were attributed to “metabolic imbalance” and “drug overdose” (39% ACD-ITD versus 30% s-CPR), while “other” etiology was more prevalent in the control arm (26% ACD-ITD versus 33% s-CPR). The justifications for the cited adjudications were multiple, but many involved the following:

- traumatic arrest
- respiratory arrest leading to cardiac arrest
- hyperglycemia/hypoglycemia in diabetic patients leading to cardiac arrest
- hyperkalemia/hypokalemia in chronic renal insufficiency patients leading to cardiac arrest
- presence of medication or drug overdoses

FDA performed a focused examination of line data for those patients adjudicated as having “non-cardiac” etiology on the basis of metabolic abnormalities or drug overdoses, since we believe that the presence of baseline parameters such as a drug abuse history or co-

existing metabolic disease/derangement at the time of the arrest cannot conclusively preclude a cardiac etiology for that arrest. Importantly, the approved protocol specifically intended for medication/drug overdose etiologies to be part of the mITT analysis population for the primary endpoint (G050062/Supplement 9, dated April 20, 2006), though the sponsor states that this aspect of the protocol was never implemented. It appears to FDA that the CEC and the sponsor employed a conservative approach to confirming a “cardiac” etiology for ITT patients. Accordingly, the principal results of the study derive from a very specific subset of cardiac arrest patients, i.e., those patients definitively lacking certain comorbidities and/or characteristics that could precipitate or facilitate the occurrence of cardiac arrest.

As is presented later, primary endpoint results for the trial arms lacked a statistically significant difference when calculated using the broader ITT population (two sided $p=0.057$). A *post hoc* primary endpoint sub-group analysis of medication/drug overdose patients, demonstrated higher endpoint success in the s-CPR arm (10/65 (15.4%)) than in the ACD-ITD arm (9/97 (9.3%)). Inclusion of the overdose patients in the mITT population, as was specified by the approved protocol, would have led to a loss of the statistical significance of the primary endpoint (two-sided $p=0.065$).

There may be patient selection factors in the presented mITT dataset that could affect the generalizability of the results to a more broadly characterized population of the type to be reasonably expected during marketed use. As such, we anticipate that if approval of the ResQCPR™ System is granted on the basis of this trial’s data, the post-marketing experience will involve substantial use in the ITT population (for example, cardiac arrest secondary to drug overdose), since we feel it is neither reasonable nor practical to expect rescuers to accurately elucidate the arrest etiology in order to assure that device use is restricted to arrest of cardiac etiology.

Schedule of Data Acquisition

SCHEDULE OF NEUROLOGIC ASSESSMENTS FOR RESQ TRIAL

| Endpoint | Modified Rankin Scale (MRS) | Cerebral Performance Category (CPC)/ Overall Performance Category (OPC) | Health Utilities Index 3 (HUI3) | Disability Rating Scale (DRS) | Cognitive Abilities Screening Instrument (CASI) | Trail-Making Test (TMT) | Beck Depression Inventory II (BDI-II) | Mayo-Portland Adaptability Inventory-4 (MPAI-4) | Quality of Life Survey (QOLS) |
|------------------------------|--|---|---|-------------------------------|---|---|---------------------------------------|---|-------------------------------|
| Estimated time to administer | 10 min. | 10 min. | 10 min. | 10 min. | 20 min. | 10 min. | 10 min. | | 15 min. |
| Form(s) | ACSI Form (1 p. pdf); optional: interview worksheet pp. 5-9, pdf | ACSI Form (1 p. pdf) | HUI3 Questionnaire Subject or Proxy vers. (7 p. pdf) & ACSI Form (2 p. pdf) | ACSI Form (1 p. pdf) | CASI E-1.1 Form (4 p. + 1 p. scoring sheet pdf) | ACSI Form (1 p. pdf); TMT forms A & B (2 p. original) | BDI-II Form (2 p. original) | MPAI-4 Form (3 p. + 1 p. scoring sheet pdf) | ACSI Form (2 p. pdf) |
| Hospital Discharge | XX | X | X | | | | | | |
| 30-day Survival | | X | X | X | | | | | |
| 90-day Survival | | X | X | X | X | X | X | X | |
| 1-year Survival | | X | X | X | X | X | X | | X |

XX – Primary endpoint

Adherence to the follow-up protocol

Adherence to the follow-up protocol is indicated in the following table:

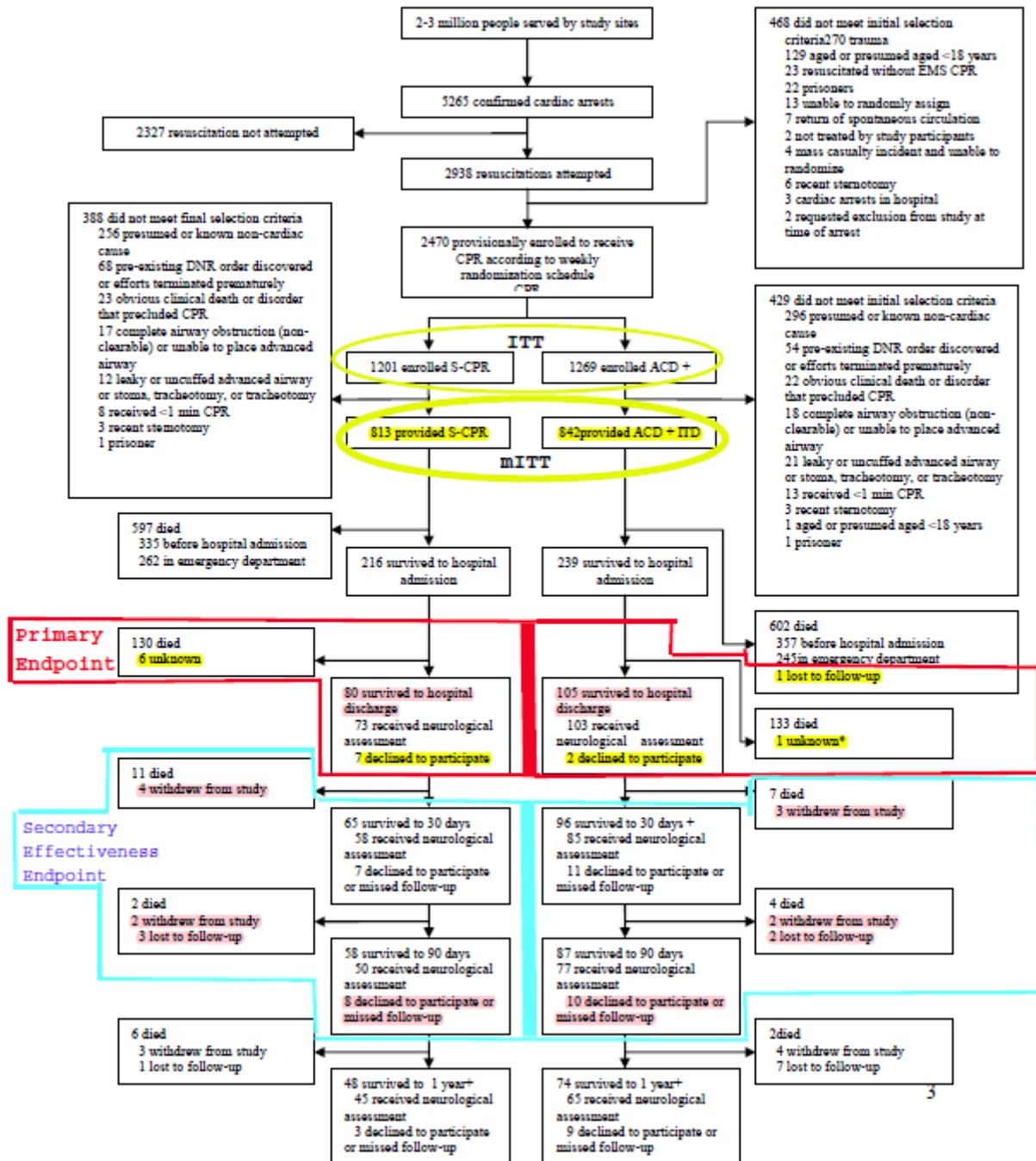
Table A. Subject Accountability by Site- Pivotal Phase¹ [N= 2470 subjects randomized in pivotal phase, who met the initial selection criteria. Includes S-CPR and ACD+ITD study arms. Number in parentheses denotes subjects who also met final selection criteria (e.g. the modified intention-to-treat population).]

| Site | enrolled subjects | Hospital Discharge ¹ | | | 30 Days ² | | | 90 Days ³ | | | 1-Year ⁴ | | |
|---------------------------|-------------------|--|------------------|----------------|---------------------------------------|-----------|----------------|-------------------------------------|-----------|----------------|----------------------------------|-----------|----------------|
| | | died pre-hospital, in-hospital, or unknown | discharged alive | with follow-up | died after discharge & before 30 days | alive | with follow-up | died after 30 days & before 90 days | alive | with follow-up | died after 90 days & before 1 yr | alive | with follow-up |
| 01 | 359 (244) | 304 (206) | 55 (38) | 53 (36) | 3 (1) | 49 (35) | 43 (23) | 0 (0) | 46 (32) | 38 (25) | 5 (2) | 38 (27) | 33 (23) |
| 02 | 532 (324) | 469 (285) | 63 (39) | 61 (37) | 3 (3) | 53 (35) | 45 (31) | 2 (1) | 47 (31) | 38 (27) | 9 (2) | 36 (28) | 34 (26) |
| 03 | 340 (206) | 299 (181) | 41 (25) | 36 (24) | 1 (0) | 37 (25) | 34 (24) | 1 (1) | 33 (22) | 31 (21) | 3 (2) | 29 (19) | 27 (18) |
| 04 | 523 (397) | 475 (359) | 48 (38) | 48 (38) | 12 (11) | 34 (26) | 26 (23) | 2 (2) | 28 (23) | 22 (20) | 2 (0) | 21 (18) | 17 (17) |
| 05 | 106 (86) | 91 (72) | 15 (14) | 11 (11) | 2 (2) | 10 (10) | 8 (8) | 1 (1) | 9 (9) | 8 (8) | 1 (1) | 7 (7) | 5 (5) |
| 06 | 469 (318) | 436 (297) | 33 (21) | 33 (21) | 2 (1) | 30 (20) | 26 (18) | 2 (1) | 27 (19) | 24 (17) | 2 (1) | 22 (15) | 18 (13) |
| 07 | 141 (80) | 123 (70) | 18 (10) | 17 (9) | 1 (0) | 16 (10) | 14 (9) | 0 (0) | 14 (9) | 14 (9) | 0 (0) | 11 (8) | 9 (8) |
| TOTAL overall | 2470 (1655) | 2197 (1470) | 273 (185) | 262 (176) | 24 (18) | 229 (161) | 196 (143) | 8 (6) | 204 (145) | 175 (127) | 22 (8) | 164 (122) | 143 (110) |
| TOTAL by group, mITT only | 1655 | 1470 | 185 | 176 | 18 | 161 | 143 | 6 | 145 | 127 | 8 | 122 | 110 |
| S-CPR | 813 | 733 | 80 | 73 | 11 | 65 | 58 | 2 | 58 | 50 | 7 | 48 | 45 |
| ACD+ITD | 842 | 737 | 105 | 103 | 7 | 96 | 85 | 4 | 87 | 77 | 1 | 74 | 65 |

The completeness of follow-up for surviving patients at each pre-specified period is commendable.

Effectiveness of Data Collection

Data availability is shown in the enrollment flow chart below:



FDA notes the following with the respect to data availability:

- 8 MITT patients had unknown survival status at discharge, and an additional 9 patients lacked mRS scoring. 76% (13 of 17) of these patients with unavailable

data precluding primary endpoint analysis were in the control arm. Control arm patients in the mITT population had a rate of primary endpoint unavailable data three times that of the treatment arm (1.6% (13/813) versus 0.5% (4/842)). There were no methods pre-specified for endpoint values imputation. Nonetheless, the mITT population should include these 17 patients. The sponsor performed a “complete case” analysis as the primary analysis by excluding these 17 subjects. In addition the sponsor performed multiple imputations to include these 17 subjects as supplementary analysis. Accordingly, FDA performed analyses based on “complete case” (CC) ($N_{ACD-ITD} = 838$ and $N_{s-CPR} = 800$) and sensitivity analyses based on all the mITT subjects ($N_{ACD-ITD} = 842$ and $N_{s-CPR} = 813$)

- The analysis of the secondary effectiveness endpoints was conditional on the subjects who survived to 90 days or 1 year. However, most subjects died before hospital discharge. In addition, by the time of the first secondary effectiveness endpoint (90 days), 21% of discharged control patients (17/80) either had withdrawn or had missing endpoint data, compared to 16% of discharged treatment patients (17/105). As a result the randomization was not preserved for the comparison between the treatment arms for the secondary effectiveness endpoints, and the estimate of the treatment may be confounded with other factors. Therefore it is difficult to interpret the comparison results in terms of the secondary effectiveness endpoint, and the p-value for the superiority test is problematic.
- Among mITT patients who survived to at least until hospital presentation (s-CPR n=478, ACD-ITD n=485), treatment arm patients comprised 56% of consents given. Enrollment to the ACD-ITD treatment arm was associated with proportionately higher active consent rate than was s-CPR randomization.

| | | Group | | Total |
|--------------------------|----------------|-------|-------------|-------|
| | | S-CPR | ACD-CPR+ITD | |
| Subject/Family Consented | Count | 141 | 180 | 321 |
| | % within Group | 29.5% | 37.1% | 33.3% |

As is shown later, consenting was associated with a higher rate of primary endpoint success, while declining consent was overwhelmingly associated with the failure to have met the endpoint. 90 mITT patients or their families declined consent. 60% of the patients who refused consent had been randomized to the s-CPR arm.

| | | Group | | Total |
|---------------------------|----------------|-------|-------------|-------|
| | | S-CPR | ACD-CPR+ITD | |
| Subject / Family Declined | Count | 54 | 36 | 90 |
| | % within Group | 11.3% | 7.4% | 9.3% |

In 74 of these 90 declined consent cases, the primary endpoint was able to be determined because mRS scoring had already been performed

Neurological Assessments

All neurological assessments (and adverse events evaluations) were to have been performed by a trained clinician “blinded to the method of CPR the subject received.” Monitoring by the sponsor’s data coordinating center (both throughout the course of the trial and then again in 2010) resulted in changes to the site-assigned modified Rankin Scores at discharge for 15 pivotal arm (ITT) patients (and 2 run-in patients). Twice as many mRS database changes (10) were made to the ACD-ITD arm as compared to the s-CPR arm (5). The changes were made to the database up to 3½ years after the index event; the blinded clinicians did not appear to FDA to have been involved with these mRS data modifications.

The mRS changes in the database, which, as shown later, favored the treatment arm’s effectiveness profile, were made at times when the sponsor was effectively unblinded to aggregate results and was unblinded to patient specific data. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

Protocol Deviations

Protocol deviations were compiled by medical monitors (employees of the sponsor). The sponsor categorized the protocol deviations as either “major” or “minor” based upon *post hoc* determination of whether they “may have impacted the primary effectiveness and safety endpoint.” There was no hierarchical score assigned to severity of protocol deviations. Most of the deviation categories were related to the study devices and thus involved treatment-arm subjects only. Major protocol deviation rates ranged from 10.5% at Site 5 to 43.8% at Site 7.

Site 06 had the highest number of major protocol deviations (76). 80% of that site’s deviations (61) transpired in the field before hospital arrival. Thus Site 06 had the both the highest number and highest proportion of in-field major deviations among sites.

Performing pre-specified neurological assessments out-of-window was the most prevalent major protocol violation.

Table D. Protocol Deviations: Follow-up Completed Outside Window [pivotal phase, mITT]*

| | Hospital Discharge | | 30 Days | | 90 Days | | 1 year | |
|--------------|--------------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | S-CPR N=74 | ACD+ITD N=101 | S-CPR N=58 | ACD+ITD N=84 | S-CPR N=50 | ACD+ITD N=77 | S-CPR N=45 | ACD+ITD N=65 |
| Site 1 | 9/20 (45.0) | 5/15 (33.3) | 4/18 (22.2) | 1/11 (9.1) | 3/16 (18.8) | 4/9 (44.4) | 2/14 (14.3) | 1/9 (11.1) |
| Site 2 | 5/14 (35.7) | 7/23 (30.4) | 1/9 (11.1) | 4/22 (18.2) | 5/8 (62.5) | 7/19 (36.8) | 1/9 (11.1) | 4/17 (23.5) |
| Site 3 | 2/13 (15.4) | 1/12 (8.3) | 3/13 (23.1) | 2/11 (18.8) | 2/11 (18.2) | 5/10 (50.0) | 4/9 (44.4) | 0/9 |
| Site 4 | 0/16 | 1/22 (4.5) | 0/9 | 4/14 (28.6) | 3/7 (42.9) | 8/13 (61.5) | 3/7 (42.8) | 3/10 (30.0) |
| Site 5 | 1/6 (16.7) | 2/4 (50.0) | 0/4 | 2/4 (50.0) | 0/4 | 1/4 (25.0) | 0/3 | 1/2 (50.0) |
| Site 6 | 1/3 (33.3) | 2/18 (11.1) | 1/3 (33.3) | 1/15 (6.7) | 1/2 (50.0) | 4/15 (26.7) | 1/2 (50.0) | 3/11 (27.3) |
| Site 7 | 1/2 (50.0) | 0/7 | 2/2 (100.0) | 5/7 (71.4) | 2/2 (100.0) | 5/7 (71.4) | 1/1 (100.0) | 2/7 (28.6) |
| TOTAL | 19/74 (25.7) | 18/101 (17.8) | 11/58 (19.0) | 19/84 (22.6) | 16/50 (32.0) | 34/77 (44.2) | 12/45 (26.7) | 14/65 (25.0) |

*N= number of subjects with follow-up at each interval shown (completed at least one assessment). Data shown are number of subjects with follow-up completed outside window/number of subjects with follow-up (% of subjects with follow-up at interval)

FDA is not able to gauge the extent, if any, to which the neurological endpoint data collected outside of the pre-specified windows may have resulted in inaccurate assessments. In general, FDA believes that retrospective data entry tends to adversely affect the accuracy of a time-dependent measurement such as the neurological assessment scores specified by the protocol. We do note with some concern that over 25% of control arm patients included for the primary endpoint analysis appear to have received some or all of the specified assessments outside of the 5 days post-discharge window. Most importantly, FDA is concerned that mRS assignments were made and/or changed in the absence of data collected from the time-specific structured interviews.

Randomization errors

“Randomization error” was defined *post hoc* by the sponsor as a “failure to stock vehicles with study devices during a device week (i.e., as per the weekly randomization schedule)”. Some control arm patients may have been inappropriately resuscitated with one or both of the study devices:

Table B. Protocol Deviations: Randomization Error [pivotal phase, mITT]

| | S-CPR | ACD+ITD | TOTAL |
|--------------|-----------|-----------|-----------|
| Site 1 | 1 | 1 | 2 |
| Site 2 | 1 | 1 | 2 |
| Site 3 | 2 | 2 | 4 |
| Site 4 | 2 | 6 | 8 |
| Site 5 | 0 | 0 | 0 |
| Site 6 | 3 | 1 | 4 |
| Site 7 | 1 | 0 | 1 |
| TOTAL | 10 | 11 | 21 |

Other improper use of the device

There were at least 47 instances of “Other improper use of the device” including a minimum of 16 treatment arm patients in whom one or both study devices (i.e., the System as a whole) were not in fact used because of what were considered “valid, appropriate reasons“.

43 of the 53 violations in which the treatment arm patients did not receive the ITD came from the top 3 enrolling sites:

Table 1 ITD protocol violations per site

| Site | ACD-ITD enrollment (mITT) | Cases in which ITD not used | Proportion of Site’s treatment arm population |
|------|---------------------------|-----------------------------|---|
| 02 | 169 | 13 | 8% |
| 04 | 208 | 16 | 8% |
| 06 | 169 | 14 | 8% |

In total, FDA believes that a substantial number of randomized patients were in fact not fully treated in the manner implied by their randomization assignments,

Table 2 Number of Patients with Study Devices Used by Study Group [pivotal phase, mITT] (by the sponsor)

| Number of devices used | s-CPR (N=813) | ACD-ITD (N=842) |
|------------------------|---------------|-----------------|
| 0 | 803 | 28 |
| 1 (1 ITD or 1 ACD) | 5 | 32 |
| 2 (1 ITD and 1 ACD) | 5 | 782 |

FDA requested an adjunctive analysis of the primary endpoint on a “per protocol” basis. This analysis was pre-specified, however, the definition for the analysis population was not.

This “per-protocol” analysis provided endpoint results (two-sided $p=0.035$) that were supportive of the primary mITT analysis. The post hoc defining of the population, particularly with its subjective inclusion of patients for whom “devices were not used for valid reasons”, is prone to introducing bias, however. To address potential bias issues, FDA utilized post hoc “as-treated” analyses presented later.

In general, FDA considers as-treated analyses to be very informative with interpretation of superiority trials comparing device treatment to an existing standard-of-care treatment (since as-treated analyses evaluates the treatment effect based on the actual received treatment rather than the assigned treatment). For this trial, FDA’s review of treatment-arm patients’ line data identified several instances of treatment-arm statistical successes that clinically seemed more consistent with control-arm success. As presented below, the *post-hoc* adjunctive analyses were not always consistent with the mITT primary analysis.

Patient Demographics and Characteristics

Baseline Demographics

Statistically significant differences in baseline demographics between the two arms were not detected at significance level of 0.05:

Table 15.1 Baseline Characteristics, mITT¹
(modification of Table 24 submitted in original PMA, with p-values added)

| Parameter | S-CPR (N=813) | ACD+ITD (N=840) | P value |
|---|------------------|--------------------|---------|
| Age, years (mean +/- SD) | 66.8 ± 14.5 | 67.0 ± 15.2 | 0.798 |
| 15-24 years | 1 (0.1) | 3 (0.4) | |
| 25-34 years | 11 (1.4) | 8 (1.0) | |
| 35-44 years | 36 (4.4) | 47 (5.6) | |
| 45-54 years | 114 (14.0) | 133 (15.8) | |
| 55-64 years | 215 (26.4) | 179 (21.3) | |
| 65-74 years | 172 (21.2) | 169 (20.1) | |
| 75-84 years | 162 (19.9) | 192 (22.9) | |
| ≥85 years | 102 (12.5) | 109 (13.0) | |
| Male | 539 (66.3) | 558 (66.4) | 0.959 |
| Race: | | | 0.174 |
| White | 660 (81.2) | 713 (84.9) | |
| Asian | 31 (3.8) | 19 (2.3) | |
| Native Hawaiian/ Pacific Islander | 3 (0.4) | 1 (0.1) | |
| American Indian/Alaska Native | 9 (1.1) | 10 (1.2) | |
| Black/African American | 94 (11.6) | 88 (10.5) | |
| Unknown | 16 (2.0) | 9 (1.1) | |
| Ethnicity: | | | 0.485 |
| Hispanic/Latino | 15 (1.8) | 19 (2.3) | |
| Not Hispanic/Latino | 782 (96.2) | 810 (96.4) | |
| Unknown | 16 (2.0) | 11 (1.3) | |
| Bystander witnessed arrest | 383 (47.2) | 398 (47.4) | 0.987 |
| EMS witnessed arrest | 76 (9.4) | 80 (9.5) | |
| Unwitnessed arrest | 353 (43.5) | 361 (43.0) | |
| Not available | 1 (0.1) | 1 (0.1) | |
| First CPR by: | | | 0.744 |
| Bystander CPR | 350 (43.1) | 356 (42.4) | |
| EMS | 462 (56.8) | 484 (57.6) | |
| Unknown | 1 (0.1) | 0 (0.0) | |
| Initial arrest rhythm: | | | 0.151 |
| Ventricular fibrillation/pulseless ventricular tachy | 247 (30.4) | 292 (34.8) | |
| Asystole | 379 (46.6) | 375 (44.6) | |
| Pulseless electrical activity | 180 (22.1) | 170 (20.2) | |
| Not available | 7 (0.9) | 3 (0.4) | |
| 911- to- first response, minutes (mean ± SD) | 5.3 ± 2.8 | 5.3 ± 3.0 | 0.801 |
| 911-to- EMS CPR, minutes (mean ± SD) ² | 6.6 ± 3.4 | 6.7 ± 3.2 | 0.768 |
| 911-to- first study device placed, minutes (mean ± SD) ² | - | 7.1 ± 3.5 | - |

(Source: Appendix 13c. Listing 1- age, mean; Listing 2- age, categories; Listing 3- gender; Listing 4- race; Listing 5- ethnicity; Listing 10- witnessed arrest; Listing 11- bystander CPR; Listing 12- initial rhythm; Listing 13- 911 to first response; Listing 15- 911 to EMS CPR; Listing 15.5- 911 to first device)

¹Numbers shown are subjects (%), unless otherwise indicated.

²Data do not include arrests witnessed by EMS personnel

The trial enrolled Hispanic/Latino patients at a proportion substantially less than the proportion of Hispanics/Latinos in the U.S. (2.1% compared to 16.3%).

Comparability of Treatment and Control Groups

Comparability of the two groups was also evaluated with an analysis of the following pre-specified covariates:

- Age
- Gender
- Witnessed vs. unwitnessed cardiac arrest

- Time from collapse to CPR for arrest: < 10 minutes, ≥ 10 minutes
- Initial recorded rhythm: VT/VF vs. Other rhythms
- Airway secured vs. unable to secure (secured vs. unsecured)
- Cause of death: presumed cardiac vs. presumed non-cardiac

Unadjusted p-values were >0.10 for all covariates when comparing the mITT groups, except for the initial recorded rhythm. The control arm had a lower proportion of VF/VT than the treatment arm.

Table 22.10 Initial Arrest Rhythm (mITT)

| | | | Group | | Total |
|-----------------------|---------|----------------|-------|-------------|-------|
| | | | S-CPR | ACD-CPR+ITD | |
| Initial arrest rhythm | VF / VT | Count | 247 | 292 | 539 |
| | | % within Group | 30.6% | 34.8% | 32.8% |

For both arms, VF/VT rhythms were more frequent in the broader ITT population, but the arms were more balanced.

Table 22.9 Initial Arrest Rhythm (ITT)

| | | | Group | | Total |
|-----------------------|---------|----------------|-------|-------------|-------|
| | | | S-CPR | ACD-CPR+ITD | |
| Initial arrest rhythm | VF / VT | Count | 294 | 335 | 629 |
| | | % within Group | 24.8% | 26.8% | 25.8% |

Cardiac arrests of VF/VT etiology typically have more favorable rates of ROSC and survival than arrests presenting with asystole or PEA. In that context, FDA notes that final inclusion/exclusion criteria led to the removal of 20% of s-CPR ITT VF/VT successes from the mITT primary endpoint analysis (50 patients to 40 patients), whereas only 7% of the ACD-ITD ITT VF/VT successes were excluded from the mITT population (71 patients to 66 patients).

Use of the System in the field (mITT patients)

| | ACD+ITD (N= 840) |
|--|------------------|
| ITD treatment duration, minutes (Mean ± SD) | 28.4 ± 11.9 |
| ≤ 1 min | 1 (0.1) |
| >1 min and ≤ 5 min | 24 (2.9) |
| > 5 min and ≤ 10 min | 46 (5.5) |
| > 10 min and ≤ 20 min | 116 (13.8) |
| > 20 min and ≤ 30 min | 272 (32.4) |
| > 30 min | 329 (39.2) |
| Not available/not applicable ² | 52 (6.2) |
| ACD CPR treatment duration, minutes (Mean +/- SD) | 28.0 ± 11.5 |
| ≤ 1 min | 1 (0.1) |
| >1 min and ≤ 5 min | 24 (2.9) |
| > 5 min and ≤ 10 min | 43 (5.1) |
| > 10 min and ≤ 20 min | 136 (16.2) |
| > 20 min and ≤ 30 min | 263 (31.3) |
| > 30 min | 339 (40.4) |
| Not available/not applicable ³ | 34 (4.0) |
| ITD attachment- | |
| To facemask | 717 |
| To endotracheal tube | 586 |
| To supraglottic airway (e.g., combitube, laryngeal mask airway) | 169 |
| ACD CPR device- | |
| Suction difficulty | 81(9.6) |
| Device use discontinued | 8 |
| due to: | |
| breast size | 10 |
| hair | 13 |
| diaphoresis | 16 |
| chest shape | 14 |
| other/unknown | 40 |

The majority of treatment arm mITT patients were treated with the ITD and/or ACD for more than 20 minutes; over half of these patients were never transported to the hospital.

Patients' In-hospital Characteristics

In aggregate, the use of key adjunctive in-hospital therapies was not statistically significantly different between arms.

Table 28 In-hospital Treatment and Neurologic Outcomes at Hospital Discharge, mITT¹

| | S-CPR (N=813) | ACD+ITD (N=840) | P value |
|--|------------------|--------------------|---------|
| Admitted to hospital | 216 (26.6) | 237 (28.2) | 0.474 |
| Survived to 24 hrs following arrest | 176 (21.6) | 197 (23.6) | 0.410 |
| Not available | 9 | 6 | |
| Return of spontaneous circulation, in emergency dept (if arrested in emergency dept) | 284 (59.4) | 306 (63.4) | 0.233 |
| In-hospital hypothermia (% admitted) | 85 (39.4) | 92 (38.8) | 0.923 |
| Cardiac catheterization (% admitted) | 72 (33.3) | 100 (42.2) | 0.053 |
| coronary stenting (% admitted) | 28 (13.0) | 38 (16.0) | 0.424 |
| Implanted cardioverter-defibrillator (% admitted) | 30 (13.9) | 41 (17.3) | 0.366 |
| Pacemaker placed (% admitted) | 3 (1.4) | 2 (0.8) | 0.673 |
| Coronary bypass surgery (% admitted) | 6 (2.8) | 15 (6.3) | 0.078 |
| Made DNR after admission (% admitted) | 95 (44.0) | 108 (45.6) | 0.080 |
| Survival to hospital discharge | 80 (9.9) | 104 (12.4) | 0.118 |
| Not available | 6 | 2 | |

The 2 key interventions, which had the most balanced utilization (therapeutic hypothermia (two-sided p=0.923)) and the least balanced utilization (cardiac catheterization during the index hospitalization (two-sided p=0.053)) are discussed below.

The use of in-hospital therapeutic hypothermia (TH) was similar in both arms of the trial (~11% of mITT patients overall, 39% of mITT patients admitted to the hospital). Stratified by TH, patient variables between the two arms were comparable.

Table A: Subjects with and without Adjuvant In-Hospital Therapeutic Hypothermia: Patient Demographics and Pre-Hospital Resuscitation Efforts [mITT]

| | S-CPR (n=216) | | ACD+ITD (n=239) | |
|--|-------------------|--|--------------------|--|
| | With TH (n=85) | Admitted and without confirmed TH (n=131) | With TH (n=93) | Admitted and without confirmed TH (n=146) |
| Age, mean +/- SD | 61.02 ± 14.97 | 67.47 ± 14.98 | 60.71 ± 14.24 | 66.86 ± 16.11 |
| Age, years: | | | | |
| 18-34 | 4 (4.7) | 2 (1.5) | 3 (3.3) | 2 (1.4) |
| 35-44 | 7 (8.2) | 5 (3.8) | 6 (6.5) | 8 (5.5) |
| 45-54 | 19 (22.4) | 19 (14.5) | 23 (25.0) | 25 (17.1) |
| 55-64 | 20 (23.5) | 33 (25.2) | 25 (26.1) | 27 (18.5) |
| 65-74 | 18 (21.2) | 27 (20.6) | 19 (20.7) | 32 (21.9) |
| 75-84 | 15 (17.6) | 23 (17.6) | 13 (14.1) | 28 (19.2) |
| ≥ 85 | 2 (2.4) | 22 (16.8) | 4 (4.3) | 24 (16.4) |
| Data not available | 0 | 0 | 0 | 0 |
| Gender, male | 58 (68.2) | 74 (56.5) | 64 (68.5) | 96 (65.8) |
| Arrest witnessed | 27 (31.8) | 37 (28.2) | 26 (28.3) | 37 (25.3) |
| Arrest unwitnessed | 58 (68.2) | 94 (71.8) | 67 (71.7) | 108 (74.0) |
| Data not available | 0 | 0 | 0 | 1 (0.7) |
| Bystander CPR provided | 37 (43.5) | 62 (47.3) | 32 (33.7) | 55 (37.4) |
| Data not available | 0 | 0 | 0 | 0 |
| Initial cardiac arrest rhythm: | | | | |
| Ventricular fibrillation/pulseless ventricular tachycardia | 55 (64.7) | 56 (42.7) | 66 (71.7) | 75 (51.4) |
| Asystole | 19 (22.4) | 40 (30.5) | 17 (17.4) | 41 (28.1) |
| Pulseless electrical activity | 9 (10.6) | 33 (25.2) | 9 (9.8) | 29 (19.9) |
| Data not available | 2 (2.4) | 2 (1.5) | 1 (1.1) | 1 (0.7) |
| 911 to first response time, minutes, mean ± SD | 5.22 ± 2.46 | 5.05 ± 2.16 | 5.27 ± 4.63 | 4.93 ± 2.55 |
| 911 to EMS CPR start time, minutes ¹ | 5.47 ± 3.00 | 5.97 ± 3.13 | 5.30 ± 2.97 | 5.08 ± 3.05 |
| 911 to placement of study device, minutes ¹ mean ± SD | - | - | 5.67 ± 3.28 | 5.77 ± 3.07 |
| ROSC during pre-hospital CPR | 82 (96.5) | 127 (96.9) | 88 (94.6) | 134 (91.8) |
| Epinephrine (1:10,000), mg mean dose ± SD | 2.54 ± 1.61 | 2.73 ± 1.77 | 2.61 ± 1.73 | 2.69 ± 1.62 |
| patients without ROSC | 3.67 ± 0.58 | 2.50 ± 1.29 | 3.80 ± 3.11 | 3.90 ± 1.79 |
| Duration of CPR, minutes mean ± SD | 16.65 ± 10.47 | 17.72 ± 11.03 | 18.01 ± 10.06 | 18.08 ± 10.80 |
| Duration CPR, patients without ROSC | 41.0 ± 12.12 | 28.75 ± 2.06 | 28.4 ± 11.01 | 30.42 ± 9.80 |

The rate of cardiac catheterization among admitted mITT patients was higher in the treatment arm (42% versus 33%), though the difference was not statistically significant. The rates of subsequent therapeutic intervention (PCI or CABG) among catheterized

patients were more similar (47% (s-CPR) and 53% (ACD-ITD)). Baseline characteristics of the PCI/CABG sub-groups were clinically comparable.

Table C:
Subjects who Received Coronary Stenting OR Coronary Bypass surgery:
Patient Demographics and Pre-Hospital Resuscitation Efforts [mITT]

| | S-CPR (n=34) | ACD-ITD (n=53) |
|--|-----------------|-------------------|
| # patients with coronary stenting | 28 | 38 |
| # patients with coronary bypass surgery | 6 | 15 |
| Age, years mean +/- SD | 58.06 ± 14.19 | 59.46 ± 13.38 |
| 18-34 | 2 (5.9) | 1 (1.9) |
| 35-44 | 2 (5.9) | 5 (9.4) |
| 45-54 | 10 (29.4) | 14 (26.4) |
| 55-64 | 10 (29.4) | 14 (26.4) |
| 65-74 | 6 (17.6) | 11 (20.8) |
| 75-84 | 3 (8.8) | 7 (13.2) |
| ≥ 85 | 1 (2.9) | 1 (1.9) |
| Data not available | 0 (0.0) | 0 (0.0) |
| Gender, male | 30 (88.2) | 40 (75.5) |
| Arrest witnessed | 26 (76.5) | 43 (81.1) |
| Arrest unwitnessed | 8 (23.5) | 10 (18.9) |
| Data not available | 0 (0.0) | 0 (0.0) |
| Bystander CPR provided | 23 (67.6) | 18 (34.0) |
| Data not available | 0 (0.0) | 0 (0.0) |
| Initial cardiac arrest rhythm: | | |
| Ventricular fibrillation/pulseless ventricular tachycardia | 29 (85.3) | 47 (88.7) |
| Asystole | 2 (5.9) | 3 (5.7) |
| Pulseless electrical activity | 1 (2.9) | 3 (5.7) |
| Data not available | 2 (5.9) | 0 (0.0) |
| 911 to first response time, minutes | 4.68 ± 2.52 | 4.72 ± 2.17 |
| 911 to EMS CPR start time, minutes ² | 6.03 ± 5.03 | 7.03 ± 5.48 |
| 911 to placement of study device, minutes | - | 6.33 ± 4.33 |
| ROSC during pre-hospital CPR | 34 (100.0) | 49 (92.5) |
| Epinephrine (1:10,000), mg | 2.24 ± 1.35 | 2.59 ± 1.58 |
| patients without ROSC | n/a | 3.25 ± 0.96 |
| Duration of CPR, minutes | 12.32 ± 8.57 | 15.77 ± 10.22 |
| Duration CPR, patients without ROSC | n/a | 28.00 ± 7.79 |
| Admitted to hospital | 34 (100.0) | 53 (100.0) |
| Coronary stenting | 27 (79.4) | 38 (71.7) |
| Coronary bypass surgery | 7 (20.6) | 15 (28.3) |
| Implanted cardio-defibrillator, % of admitted | 11 (32.4) | 12 (22.6) |

There was, however, considerable variability between sites on the use of therapeutic hypothermia for enrolled patients. Site 06 enrolled ~19% of the mITT population (18% of s-CPR and 20% of ACD-ITD). Baseline characteristics of patients from Site 06 did not seem to differ substantially from the mITT cohort as a whole. However, Site 06 utilized therapeutic hypothermia and cardiac catheterization for admitted patients substantially less often than the study overall (23% vs. 39% and 26% vs. 38% respectively). Most pronounced, control arm patients at Site 06 received therapeutic hypothermia, catheterization, coronary stenting, and coronary bypass surgery at rates less than half of the pooled sites' utilization rates.

| | Site 06 | | Main Study | |
|---|------------------|--------------------|------------------|--------------------|
| | S-CPR (n=149) | ACD+ITD (n=169) | S-CPR (n=813) | ACD+ITD (n=840) |
| Admitted to hospital | 31 (20.8) | 44 (26.0) | 216 (26.6) | 237 (28.2) |
| Cardiac catheterization (% admitted) | 4 (12.9) | 16 (36.4) | 72 (33.3) | 100 (42.2) |
| Coronary stenting (% admitted) | 1 (3.2) | 7 (15.9) | 28 (13.0) | 38 (16.0) |
| Coronary bypass surgery (% admitted) | 0 | 3 (6.8) | 6 (2.8) | 15 (6.3) |
| Implanted cardio-defibrillator (% admitted) | 0 | 5 (11.4) | 30 (13.9) | 41 (17.3) |
| In-hospital hypothermia (% admitted) | 6 (19.4) | 11 (25.0) | 85 (39.4) | 92 (38.8) |

As shown later, use of in-hospital therapeutic hypothermia and coronary revascularization interventions appeared to have substantial beneficial effects for patients in both arms. Use of hypothermia was also associated with a substantial narrowing of the investigational device's treatment effect. Site 06, with the lowest rate of therapeutic hypothermia utilization, generated a treatment effect (primary endpoint success rate differential) substantially greater than any other site.

Monitoring and Clinician Blinding

Clinician Blinding

Because the devices were used in the field during CPR, it was not possible to blind the emergency medical service personnel to the CPR method. However, evaluation of the Rankin Score (mRS) at the time of hospital discharge and neurological assessments for the secondary endpoint was planned to be performed by healthcare professionals who were blinded to the treatment assignment. The physicians evaluating possible adverse events during hospitalization were also to be blinded to the treatment assignment.

§50.24 Waiver of Informed Consent for Emergency Research

As noted above, the ResQTrial met the regulatory requirements to perform the study under §50.24 Waiver of Informed Consent Requirements in Emergency Research. There were several documents available both prior to enrollment into the ResQTrial as well as during the study (61 FR 51529, October 2, 1996; and Guidance for Sponsor's, Clinical Investigators, and IRBs – Data retention when subjects withdraw from FDA-Regulated Clinical Trials, October 2008) that clearly indicated that all patients are considered enrolled into the study (ITT population), and all data collected on the enrolled patient, up to the point of withdrawal (if this occurs) are to remain in the study.

However, the sponsor indicates that the 21 CFR 50.24 Waiver of Informed Consent Requirements in Emergency Research regulation was interpreted by the study sites, IRBs and sponsor, in such a way that the patient's medical record could not be reviewed for the study (i.e., data could not be included in the study) without informed consent. The sponsor further notes that the issuance of the October 2008 FDA Guidance Document (Data Retention when Subjects Withdraw from FDA-Sponsored Clinical Trials) was used in an attempt to gain access to the patient's medical records and complete data collection and obtain endpoint information.

Unfortunately, this is not the intent of the regulation. The pre-amble and FDA response to comment 95 found in the final rule for §50.24 (61 FR 51529, October 2, 1996) both clearly indicate that data are to be collected up to the point of patient withdrawal from the study, and that the data up to that point must remain as part of the study.

The sponsor states that they utilized the October 2008 FDA Guidance Document to retrospectively complete files and obtain study data (a letter to IRBs petitioning for retrospective review based on the 2008 FDA Guidance is dated February 2009). It should be noted that the Data Management Plan (ACSI document dated November 9, 2005) clearly states that the CRF data will be "...source data verified, entered, reviewed and locked within 30 days of receipt." However, due to this retrospective review of the patient's medical record and associated revisions made to exclusion criteria, mRS scores, etc., FDA found many patient CRFs that were altered 3+ years after the event.

While many of the files remained incomplete due to absence or denial of consent, consistency for the process and appropriate use of the 2008 FDA Guidance is not clear, e.g., patient files were adjudicated late and/or retrospectively revised, thus altering the mITT population, even when consent was obtained.

FDA accepts the possibility that the §50.24 regulation may have been misinterpreted by sites and their IRBs. Nonetheless, the processes which led to obtaining retrospective data, making changes to the case report forms, primary endpoint data, and refining the mITT population, coupled with the possibility that the sponsor was effectively unblinded, should be considered in the interpretability and integrity of the study data. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded..

Trial Monitoring

Data Coordinating Center

Trial monitoring included the Data Coordinating Center (DCC). DCC monitors, who were sponsor employees, were responsible for "...continued protocol compliance, complete and accurate data collection and device accountability records, timely reporting of all study adverse events, and documentation of protocol deviations."

With regard to the management of patient line data (including endpoint data), the sponsor stated that "a decision was made at the beginning of the study for the DCC [data coordinating center] to have access to CRFs. This was a small group of persons who did not otherwise convey the unblinded information to other ACSI staff." The DCC included, among others, the sponsor's Chief Medical Officer, its Director of Clinical Trials, and its Director of Clinical Affairs. The DCC "verified and validated" all elements of the case report forms; the DCC (and thus the sponsor) also "had access to treatment assignment on an individual case-by-case basis."

Based upon the Agency's review of source CRFs, the time course of some endpoint adjudications, and the nature of some internal and external communications from the sponsor, FDA needs to consider the possibility that the integrity of essential firewalls may have been compromised over the course of the trial. It is important to note that DCC members/study monitors were company officials and had access to group specific data, and developing trial results.

Data Safety Monitoring Board

Trial monitoring included an independent Data and Safety Monitoring Board (DSMB). The DSMB met at multiple points throughout the run-in and pivotal phases. The DSMB and Sponsor both affirmed to FDA that they remained blinded to the arm-specific effectiveness results until July 2009 and May 2010 respectively. In the intervening period, the DSMB recommended substantial modifications to trial design and execution and, ultimately, enrollment cessation.

As discussed in detail above, FDA believes arm-specific results could be readily and accurately inferred from the sequential DSMB reports. FDA has never had any concerns regarding the potential for DSMB unblinding in this trial. FDA recognizes that a DSMB can and should become unblinded at any time its members feel it is necessary. However, FDA believes that the effective unblinding of the sponsor to the data could introduce significant bias and affect the interpretability of this trial's results. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

Clinical Events Committee

Trial monitoring included an independent Clinical Events Committee (CEC). The CEC was responsible for:

- adjudicating the determination of all mITT patients from the ITT (provisionally enrolled) population;
- adjudicating adverse events as major or minor; and
- adjudicating events that contributed to the secondary safety endpoint.

The CEC chose the following mechanism for event adjudication, as it was not pre-specified in the CEC charter:

Due to the large number of anticipated AEs in a study of this type, at the beginning of the study the CEC determined that AEs would be reviewed and adjudicated in batches that were prepared by the DCC (Data Coordination Center) and periodically distributed among the individual CEC members. Any AEs that were deemed controversial by the initial reviewer would then be reviewed and finally adjudicated by the full committee.

Three CEC members were affiliated with one of the clinical sites; the CEC Chairman was a member of the Emergency Medicine department of that site. FDA is concerned that these relationships could have introduced bias into some of the Committee's deliberations.

The CEC charter mandated that patient exclusion from the mITT population not be the result of a single member's review:

Using the a priori criteria defined in the protocol, the CEC will act as the final arbiter for these cases, and will determine the final disposition by majority vote.

The sponsor confirmed to FDA that all determinations regarding inclusion within the mITT analysis population had been made according to this rule. However, FDA's review of CRFs and CEC documents raised concerns related to that fact that many of the final mITT decisions had been made at dates remote from the index hospitalization, and at a time when the sponsor was effectively unblinded. For example, FDA identified 9 mITT patients initially adjudicated into the mITT population who were subsequently reevaluated at the DCC's (i.e., sponsor's) request, and excluded from mITT on the criterion of presumed overdose or metabolic abnormality. 5 of these 9 subsequently excluded patients were in the treatment arm, all having had $mRS > 3$ (endpoint failure); 4 of the 9 patients were in the control arm, and 2 of them had $mRS \leq 3$ (endpoint success). It should be noted that although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

Effective unblinding

FDA believes that "effective unblinding" of the sponsor occurred since 2006. "Effective unblinding" is defined in the following manner: at a minimum, knowledge of the delta treatment group difference between the two groups by the sponsor and use of this knowledge to impact trial decisions and/or execution. Any changes to the trial after effective unblinding will bias the trial, destroy the stringent control of Type I error and render any subsequent p-value analysis unquantifiable. Interpretation of trial results, therefore, becomes problematic.

Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

Identified Changes to Data Collection and Analysis Related to Monitoring Procedures

a. Unplanned interim looks

Trial objective, size, and format were modified, in part, on the basis of what FDA believes were unplanned interim analyses performed by the DSMB as described previously.

b. Modifications to Case Report Forms

Through its subsidiary DCC, the sponsor elicited modification to CRFs by the source sites. These changes were made months to years after original completion of the CRFs (most changes were made following the 2009 enrollment suspension). FDA identified 28 patients that were subsequently removed from the mITT cohort by the CEC on the basis of the updated CRFs. 22 of these 28 subsequently excluded patients were in the treatment arm, 21 of them (95%) having had mRS>3 (endpoint failure); 6 of the 28 patients were in the control arm, and 3 of them (50%) had mRS≤3 (endpoint success).

c. Removal of Drug/medication overdose patients

As discussed previously, the trial's protocol had been specifically modified in 2006 to include overdose patients within the mITT analysis. The sponsor states that it chose not to implement the inclusion of overdose patients, and thus the sponsor's mITT analysis excludes data contributions from 163 pivotal patients with an overdose etiology. FDA acknowledges that guidance in 2006 regarding statistical requirements for labeling purposes may have contributed to this decision. Nonetheless, FDA notes that while a higher proportion of ITT patients with overdose existed in the treatment arm (7.7%) than in the control arm (5.4%), the discrete numbers of endpoint successes were similar (9 and 10, respectively). Consequently, the primary endpoint success rate for control arm overdose patients was substantially greater than that observed in treatment arm overdose patients (15.4% and 9.3%, respectively). Removing these subjects from the primary endpoint analysis resulted in a net gain in terms of a favorable treatment effect for the device arm compared to the control arm.

d. Temporally delayed assessments/re-assessments of mRS scores

FDA identified 13 pivotal arm mITT patients for whom the endpoint-determining mRS score was either modified (7 patients) or first recorded (6 patients) after the 2009 meeting date of the DSMB.

**Table 3: 13 Pivotal arm patients with changed/delayed mRS score (mITT)
(By FDA)**

| | Group | case_num | Initial mRS | Final mRS |
|---------------------------|---------|----------|-------------|-----------|
| Changed mRS | ACD-ITD | (b) (6) | 4 | 3 |
| | ACD-ITD | (b)(6) | 2 | 1 |
| | ACD-ITD | (b)(6) | 5 | 0 |
| | ACD-ITD | (b)(6) | 3 | 2 |
| | s-CPR | (b)(6) | 4 | 3 |
| | s-CPR | (b)(6) | 3 | 4 |
| | s-CPR | (b)(6) | 2 | 4 |
| Initial mRS value missing | ACD-ITD | (b)(6) | | 3 |
| | ACD-ITD | (b)(6) | | 2 |
| | ACD-ITD | (b)(6) | | 1 |
| | ACD-ITD | (b)(6) | | 3 |
| | s-CPR | (b)(6) | | 1 |
| | s-CPR | (b)(6) | | 2 |

FDA points out that these delayed mRS determinations, which appear not to have been derived from in-person, structured interviews, led to a net 6-case increase in endpoint success for the treatment arm and a net 1-case increase to the control group’s success rate.

FDA must consider the fact that these mRS changes were not based upon in-person, structured interviews and that they were made outside of pre-specified assessment windows, at a time when the Agency believes the sponsor was effectively unblinded. FDA believes that these changes present challenges when interpreting the significance of the trial results. Although the sponsor was effectively unblinded since 2006, the sponsor has stated that they were not inappropriately or completely unblinded.

6 IDE CLINICAL STUDY RESULTS

The clinical review and FDA’s inferences from it are based predominantly upon data from the IDE trial. FDA has also considered adjunctive data during our review, including the European trials and the ROC PRIMED Study (discussed in Section 3.1 above).

6.1 Overview of G050062 (the ResQ Trial)

To meet the trial objective, the protocol specified the following endpoints and analyses:

Primary effectiveness and safety endpoint (superiority): Defined as survival to hospital discharge with a good neurologic outcome in subjects experiencing out-of-hospital cardiac arrest from presumed cardiac etiology. A good neurologic outcome was defined as a modified Rankin Score (mRS) of 3 or less using the Modified Rankin Scale. The testable hypotheses in superiority format are shown

in Appendix 1.

Three powered Secondary Endpoints were also specified:

- The first, a non-inferiority safety assessment based upon major adverse event (MAE) rates, and listed in the PMA as:
 - Death
 - Cerebral bleeding
 - Bleeding requiring transfusion or surgical intervention
 - Seizures
 - Re-arrest
 - Pulmonary Edema
 - Serious rib fractures/sternal fractures
 - All internal thoracic and abdominal injuries
 - All device malfunction, defects, failures

- The second and third are superiority effectiveness assessments based on long-term neurologic function, assessed using the Cognitive Abilities Screening Instrument (CASI, Version E-1.1) at 90 days and 1 year post-cardiac arrest in surviving subjects. The hypotheses to be tested at these two survival intervals for this secondary endpoint are found in Appendix 1.

Exploratory endpoints included:

- Non-powered secondary endpoints:
 - Return of spontaneous circulation (ROCS)
 - Survival to: 1 hour; ICU admission; 24 hours; and 30, 90, and 365 days.
 - Neurologic recovery at hospital discharge, 30, 90 and 365 days post-arrest using:
 - Trail Making Test
 - Beck Depression Inventory
 - Cerebral Performance Categories (CPC) evaluation
 - Overall Performance Categories (OPC) evaluation
 - Quality of Life after 365 days

Sub-group Analyses included:

- Witnessed vs. unwitnessed cardiac arrest
- Those in witnessed arrest whose time from collapse to initiation of CPR is $<$ or \geq 10 minutes
- Initial recorded rhythm (ventricular fibrillation/pulseless ventricular tachycardia, asystole and pulseless electrical activity), including analyses of patients who do not have asystole as a presenting rhythm, and those who are

- in pulseless electrical activity (PEA) at anytime during the cardiac arrest.
- Cause of death: presumed cardiac etiology, all non-traumatic, all non-cardiac.
- Subjects who, despite efforts by EMS personnel, are unable to have their airway secured with either an endotracheal tube, a Combitube or laryngeal mask airway.
- Subjects with a known 911 call to arrival of professional first rescuers of >10 minutes and no bystander CPR was being performed at the time BLS arrived.
- Gender
- The relationship between the CASI, Trailing Making Tests, and the Beck Depression Scale, and the OPC and CPC scores.

Analysis Populations and Inclusion/Exclusion Criteria

The principal analysis population was a modified Intention-to-Treat (mITT) group which was based on the randomization assignment for those subjects who met the final inclusion and exclusion criteria (found in Section 5.1.2 above). The mITT was proposed because subjects may receive the randomized treatment under waiver of informed consent provisions and later be found not to meet enrollment requirements (e.g., Do Not Resuscitate Orders in place).

A supplemental analysis was also specified to evaluate the primary effectiveness outcome on all randomized subjects (true ITT) to the extent of available data on study outcomes.

To account for unplanned departures from the randomization schedule, an analysis was also to be performed on a treatment delivered (pre-protocol) basis.

6.2 Study Results

The original trial was set up as a three-arm trial with an s-ITD arm. In order to address multiple testing issues for the primary endpoint, a two-sided alpha of 0.022 was initially specified for the final analysis before the s-ITD arm was dropped. After dropping the s-ITD arm, FDA approved the change of the alpha level to 0.049 (two-sided). FDA came to understand the above study issues' ramifications for type I error inflation during the PMA review process. One needs to be cautious in interpreting any analysis result which may have been affected by alpha inflation issues. As such, in order to partially address our inflation concerns, FDA believes it informative to consider the trial results in the context of the original alpha level of 0.022 (two-sided). FDA acknowledges that doing so is a post-hoc approach, but further points out that it may be impossible to accurately quantify the magnitude of the alpha inflation. FDA's concerns do not apply to the secondary effectiveness endpoints.

The final mITT population excluded at least the following sets of patients, 1) 28 patients adjudicated late and removed from the mITT population for etiology, and 2) 163 medication/drug overdose patients. Additionally, since there was no pre-specified plan for imputation, the primary mITT analysis also excludes 17 patients [13 s-CPR, 4 ACD-ITD]

with missing endpoint values.

To further investigate the potential biases introduced by the trial modifications, both the sponsor and the FDA performed the primary endpoint analysis using two additional approaches:

Approach 1 (first enrolled 1400)

- analyze the first enrolled 1400 subjects, assuming the study design had not been modified

Approach 2 (inverse normal method)

- analyze all subjects using an inverse normal method (CHW method) - the CHW (Cui-Hung-Wang) is a common inverse normal method used to combine data from two stages of a trial into a single test statistic for p-value testing.

Primary endpoint

The Primary Endpoint was defined as Survival to Hospital Discharge with MRS \leq 3.

Primary Endpoint mITT Population

The following table is the analysis of the primary endpoint excluding the 17 patients with unavailable mRS values (“complete case”):

Table 4 Survival to Hospital Discharge with MRS \leq 3 (mITT) complete case (calculated by sponsor)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------------|-----------------|-----------------|------------------------|
| mITT analysis[#] | 5.88% (47/800) | 8.95% (75/838) | 0.0186 |
| First 1400 subjects | 6.0% (41/684) | 9.1% (64/704) | 0.033 |
| CHW | 5.88% (47/800)* | 8.95% (75/838)* | 0.029** |

[#]: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Primary endpoint was met for the complete case analysis at an alpha level of 0.049.

Among patients ultimately discharged from the hospital (105 treatment and 80 control), the use of the System was associated with a higher proportion of mRS \leq 3 (71% (75/105))

and 59% (47/80), respectively).

Table D. ResQTrial: In-hospital Treatment and Neurologic Outcomes at Hospital Discharge [pivotal phase, mITT]

| | s-CPR (N=813) | ACD-ITD (N=842) |
|---|--------------------------|----------------------------|
| Discharged alive (% of all subjects) | 80 (9.9) | 105 (12.5) |
| Not available | 6 | 2 |
| Hospital Discharge with MRS ≤ 3 PRIMARY ENDPOINT | 47 (5.9) | 75 (8.9) |
| MRS at hospital discharge: | | |
| 0 | 3 (0.4) | 11 (1.3) |
| 1 | 8 (1.0) | 11 (1.3) |
| 2 | 26 (3.2) | 30 (3.6) |
| 3 | 10 (1.2) | 23 (2.7) |
| 4 | 10 (1.2) | 10 (1.2) |
| 5 | 16 (2.0) | 18 (2.1) |
| 6 | 727 (89.4) | 735 (87.2) |
| Not available | 13 | 4 |

The hospital discharge rate for the control arm (9.9%) was substantially higher than the value used by the sponsor for initial sample size calculations (6%). The sponsor’s protocol had been formulated during a time when the American Heart Association (AHA) recommendation for CPR chest compressions was 80/minute; throughout the trial’s implementation, the rate recommendation was 100/minute. The ACD has a metronome designed to prompt the rescuer to deliver compressions at a rate of 80/minute. Therefore the treatment arm (ACD-ITD) patients received CPR compressions at a rate of 80/minute, while control arm (s-CPR) patients received the AHA-recommended compression rate of 100/minute. The sponsor attributed the improvement in control arm results in large part to the change in recommended compression:ventilation ratios for s-CPR

Primary Endpoint-ITT Population

The ITT population represented a broader patient cohort, in part because it included patients with metabolic abnormalities and potential drug overdoses (evaluated with a two-sided alpha of 0.022).

Table 5. Survival to Hospital Discharge with MRS ≤ 3 (ITT) complete case, (calculated by sponsor)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|------------------------|---------------------|----------------------|-----------------|
| ITT analysis# | 5.99% (71/1186) | 8.00% (101/1262) | 0.057 |
| First 2041 subjects### | 5.85% (58/991) | 8.23% (85/1033) | 0.038 |
| CHW | 5.99% (71/1186)* | 8.00% (101/1262)* | 0.066** |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

Parent ITT population to “First 1400” mITT subjects

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Table 6 In-hospital Treatment and Neurologic Outcomes at Hospital Discharge, ITT¹

| | S-CPR (N=1201) | ACD+ITD (N=1269) | P value |
|---|-----------------|------------------|--------------------------|
| Admitted to hospital | 342 (28.5) | 381 (30.0) | 0.401 |
| Hospital Discharge with MRS ≤ 3 PRIMARY ENDPOINT | 71 (6.0) | 101 (8.0) | 0.057² |
| MRS at hospital discharge | | | 0.077 ³ |
| MRS 0 | 7 | 18 | |
| MRS 1 | 12 | 18 | |
| MRS 2 | 34 | 36 | |
| MRS 3 | 18 | 29 | |
| MRS 4 | 15 | 19 | |
| MRS 5 | 28 | 28 | |
| MRS 6 (death) | 1072 | 1114 | |
| Survival at discharge not available | 6 | 5 | |
| MRS not available | 9 | 2 | |

The primary endpoint was not met for the complete case ITT analysis at an alpha level of 0.049. The nominal p-value for the first 2041 ITT subjects was less than an alpha level of 0.049, and the primary endpoint was not met (p>0.049) using the CHW method. The ITT population includes all patients enrolled, including those excluded from the mITT population (e.g., medication/drug overdose, non-cardiac etiologies, etc.), and is important because in general clinical practice, FDA believes that the ability to distinguish cardiac arrest etiologies is unlikely.

Primary Endpoint s-ITD arm (mITT) and ROC PRIMED

Data from the incomplete s-ITD arm of the original trial design were evaluated.

The rate of hospital discharge with good neurological function (primary endpoint) was 4.0% in the s-ITD arm, substantially worse than the results reported for either the ACD-ITD or s-CPR arms.

Table D. ResQ Trial: In-hospital Treatment and Neurologic Outcomes at Hospital Discharge [pivotal phase, mITT]

| | S-CPR (N=813) | ACD+ITD (N=840) | S-CPR+ITD (N=150) |
|---|------------------|--------------------|----------------------|
| Admitted to hospital | 216 (26.6) | 237 (28.2) | 33 (22.0) |
| Hospital Discharge with MRS ≤ 3 PRIMARY ENDPOINT | 47 (5.9) | 75 (9.0) | 6 (4.0) |
| MRS at hospital discharge: | | | |
| 0 | 3 (0.4) | 11 (1.3) | 0 (0.0) |
| 1 | 8 (1.0) | 11 (1.3) | 1 (0.7) |
| 2 | 26 (3.2) | 30 (3.6) | 3 (2.0) |
| 3 | 10 (1.2) | 23 (2.7) | 2 (1.3) |
| 4 | 10 (1.2) | 9 (1.1) | 2 (1.3) |
| 5 | 16 (2.0) | 18 (2.1) | 1 (0.7) |
| 6 | 727 (89.4) | 734 (87.4) | 141 (94.0) |

The separate findings from ROC PRIMED’s larger evaluation of ITD use (analogous to s-ITD) failed to identify an effectiveness benefit as compared to sham control.

Table A: Outcomes and Safety to Hospital Discharge [ROCPRIMED Trial, mITT]¹

| | Sham N=4345 | ITD N=4373 | Difference and 95% CI | p-value |
|---|-------------------|-------------------|----------------------------|-------------|
| Transported | 2451 (56.4%) | 2448 (56.0%) | -0.4% (-2.5%, 1.7%) | 0.66 |
| ROSC at ED arrival | 1206 (27.8%) | 1186 (27.1%) | -0.6% (-2.5%, 1.2%) | 0.74 |
| Admitted to hospital | 1139 (26.3%) | 1140 (26.1%) | -0.2% (-2.0%, 1.7%) | 0.58 |
| Survived to discharge | 355 (8.2%) | 357 (8.2%) | 0.0% (-1.2%, 1.1%) | 0.50 |
| Hospital Discharge with MRS ≤ 3 (primary endpoint) | 260 (6.0%) | 254 (5.8%) | -0.1% (-1.1%, 0.8%) | 0.61 |
| MRS - mean (SD) | 5.69 (1.15) | 5.69 (1.14) | 0.01 (-0.04, 0.05) | 0.42 |
| MRS score distributions: | | | | |
| 0 | 73 (1.7%) | 81 (1.9%) | | |
| 1 | 87 (2.0%) | 77 (1.8%) | | |
| 2 | 28 (0.6%) | 22 (0.5%) | | |
| 3 | 72 (1.7%) | 74 (1.7%) | | |
| 4 | 57 (1.3%) | 55 (1.3%) | | |
| 5 | 38 (0.9%) | 48 (1.1%) | | |
| 6 | 3990 (91.8%) | 4016 (91.8%) | | |

The sponsor hypothesized that “if use of ACD-ITD is found to significantly increase these survival rates, then use of the ITD with s-CPR will significantly increase survival rates as well, but to a lesser degree, when compared with s-CPR alone in patients after cardiac arrest.” FDA acknowledges that statistical comparisons to the other groups are severely limited by s-ITD’s relatively small sample size (n=150) and early termination. Nonetheless, the available data from neither s-ITD nor ROC PRIMED are consistent with the sponsor’s primary endpoint finding, and this observation is difficult for FDA to reconcile satisfactorily.

Per protocol analysis

FDA requested an adjunctive analysis of the primary endpoint on a “per protocol” basis. This analysis although pre-specified, was not prospectively defined, and the sponsor used the following *post hoc* definition:

- Subjects enrolled in the pivotal phase and met the mITT selection criteria;
- Subjects for whom there were no randomization errors;
- Subjects for whom primary endpoint data were available; and
- Subjects for whom both study devices were used, or one or both devices were not used for valid reasons.

Table B. Outcomes [per protocol population]

| | S-CPR (n=790) | ACD+ITD (n=800) |
|--|--------------------------|----------------------------|
| Survival to hospital discharge | 73 (9.2) | 96 (12.0) |
| Survival to hospital discharge with MRS ≤ 3 ¹ | 47 (5.9) | 70 (8.8) |
| Survival to hospital discharge with MRS ≤ 3 , subjects who received at least one study device or had valid reason for no devices ² | 47 (5.9) | 74/817 (9.1) |

This “per-protocol” complete case analysis provided endpoint results (two-sided $p=0.035$) that were less than an alpha of 0.049, were supportive of the primary mITT complete case analysis in which interim looks were not taken into consideration. The post hoc defining of the population, particularly with its subjective inclusion of patients for whom “devices were not used for valid reasons”, is also prone to bias. To address potential bias issues, FDA utilized post hoc “as-treated” analyses presented later.

Primary Endpoint and relationship to consent

321 mITT patients were admitted to the hospital and then affirmed consent (patient or family, including patient ^{(b)(6)} whose mRS was not available) to study participation. To have consented was associated with primary endpoint success in 35% of cases having consent. The proportion of consented s-CPR patients who had primary endpoint success was lower than the proportion in the ACD-ITD arm (30.7% versus 38.3%).

Table 7.3: Primary Study Outcome where Subject/Family Consented

| | | | Group | | Total |
|--------------------------------|--------------|----------------|--------|-------------|--------|
| | | | S-CPR | ACD-CPR+ITD | |
| Modified Rankin Score Category | MRS ≤ 3 | Count | 43 | 69 | 112 |
| | | % within Group | 30.7% | 38.3% | 35.0% |
| | MRS ≥ 4 | Count | 97 | 111 | 208 |
| | | % within Group | 69.3% | 61.7% | 65.0% |
| Total | | Count | 140* | 180 | 320 |
| | | % within Group | 100.0% | 100.0% | 100.0% |

P = 0.194 (Fisher's Exact Test, 2-sided); * Subject #03-910, MRS not available

90 mITT patients who were admitted to the hospital eventually declined consent; In 74 of those 90 cases, the primary endpoint was able to be determined because mRS scoring had been performed prior to consent refusal. To have declined consent was associated with endpoint failure in the overwhelming majority of cases.

Table 7.4: Primary Study Outcome where Subject/Family Declined

| | | | Group | | Total |
|--------------------------------|--------------|----------------|-------|-------------|-------|
| | | | S-CPR | ACD-CPR+ITD | |
| Modified Rankin Score Category | MRS ≤ 3 | Count | 1 | 2 | 3 |
| | | % within Group | 2.4% | 6.3% | 4.1% |
| | MRS ≥ 4 | Count | 41 | 30 | 71 |
| | | % within Group | 97.6% | 93.8% | 95.9% |

Although the full implications of 50.24 regarding data collection may not have been fully understood by the sponsor, investigators and IRBs, there is no indication that differences existed between groups with regard to the consent process.

Primary endpoint and adjuvant therapy

Therapeutic hypothermia

Table 8.1: Association between Primary Endpoint and Use of Post-Resuscitation, In-Hospital Therapeutic Hypothermia [mITT]

| | MRS ≤ 3 | MRS ≥ 4 | P-value (association) |
|--|--------------|--------------|-----------------------|
| Admitted, no hypothermia: | | | 0.030 ¹ |
| S-CPR group (%) | 21 (17.6) | 98 (82.4) | |
| ACD+ITD group | 42 (29.4) | 101 (70.6) | |
| Admitted, with therapeutic hypothermia: | | | 0.632 ² |
| S-CPR group | 26 (31.0) | 58 (69.0) | |
| ACD+ITD group | 33 (35.5) | 60 (64.5) | |
| Admitted, with or without therapeutic hypothermia: | | | 0.054 ³ |
| S-CPR group | 47 (23.2) | 156 (76.8) | |
| ACD+ITD group | 75 (31.8) | 161 (68.2) | |

[Source= Listings 284-286]

¹ P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.94; 95% confidence interval = 1.035, 3.705.

² P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.23; 95% confidence interval = 0.625, 2.418.

³ P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.55; 95% confidence interval = 0.989, 2.428.

The use of therapeutic hypothermia was associated with a substantial improved clinical outcome. The effect seemed most evident in the s-CPR arm. These data suggest that the difference in the primary endpoint success between the s-CPR arm and the ACD-ITD arm was much smaller in the subjects with therapeutic hypothermia than the difference in the subjects without hypothermia. However, significant interaction effect of treatment by hypothermia was not detected either at alpha level of 0.15 (p-value=0.298 from Breslow-Day test).

Cardiac interventions

Table 8.2: Association between Primary Endpoint and Use of Cardiac Catheterization [mITT]

| | MRS ≤ 3 | MRS ≥ 4 | P-value (association) |
|---------------------------------|--------------|--------------|--------------------------|
| Admitted, no catheterization: | | | 0.466 ¹ |
| S-CPR group (%) | 7 (5.3) | 125 (94.7) | |
| ACD+ITD group | 11 (8.2) | 123 (91.8) | |
| Admitted, with catheterization: | | | 0.343 ² |
| S-CPR group (%) ³ | 40 (56.3) | 31 (43.7) | |
| ACD+ITD group | 64 (64.0) | 36 (36.0) | |

[Source= Listings 287-288]

¹ P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.57; 95% confidence interval = 0.535, 4.937.

² P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.38; 95% confidence interval = 0.705, 2.686.

³ One subject in S-CPR group had an unknown MRS.

Table 8.3: Association between Primary Endpoint and Use of Coronary Stenting [mITT]

| | MRS ≤ 3 | MRS ≥ 4 | P-value (association) |
|---|--------------|--------------|--------------------------|
| Admitted to hospital, no stenting during index hospitalization: | | | 0.012 ¹ |
| S-CPR group (%) | 28 (16.0) | 147 (84.0) | |
| ACD+ITD group | 53 (26.8) | 145 (73.2) | |
| Admitted to hospital, with stenting during index hospitalization: | | | 0.451 ² |
| S-CPR group (%) | 19 (67.9) | 9 (32.1) | |
| ACD+ITD group | 22 (57.9) | 16 (42.1) | |

[Source= Listings 289, 290]

¹ P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.92; 95% confidence interval = 1.119, 3.333.

² P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 0.65; 95% confidence interval = 0.204, 2.017.

Table 8.4: Association between Primary Endpoint and Use of Coronary Artery Bypass Graft Surgery (CABG) [mITT]

| | MRS ≤ 3 | MRS ≥ 4 | P-value (association) |
|---|--------------|--------------|--------------------------|
| Admitted to hospital, no CABG during index hospitalization: | | | 0.179 ¹ |
| S-CPR group (%) | 44 (22.2) | 154 (77.8) | |
| ACD+ITD group | 62 (28.1) | 159 (71.9) | |
| Admitted to hospital, with CABG during index hospitalization: | | | 0.249 ² |
| S-CPR group (%) ³ | 3 (60.0) | 2 (40.0) | |
| ACD+ITD group | 13 (86.7) | 2 (13.3) | |

[Source= Listings 291,292]

¹ P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.37; 95% confidence interval = 0.855, 2.189.

² P value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 4.33; 95% confidence interval = 0.209, 77.97.

³ One subject in S-CPR group had an unknown MRS.

Two-thirds of patients who underwent a coronary intervention met the primary endpoint, irrespective of randomization arm.

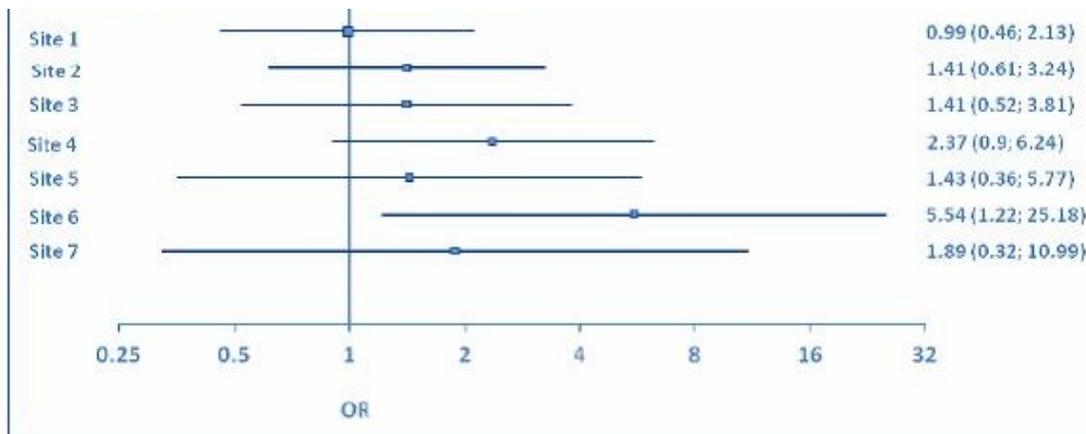
Coronary interventions were associated with better survival with good neurological outcome. These data may suggest that the device facilitates a patient's ability to undergo cardiac catheterization, thereby accruing a substantial survival benefit. However, it is also possible that the portion of the observed treatment effect accrued from increased cardiovascular intervention rates was a function of either imbalance in unrecognized covariates or unintentional bias regarding the use of the cardiovascular interventions.

Site variability for adjuvant therapy

As noted earlier, Site 06 utilized key adjuvant therapies substantially less frequently than other sites; the disparity was most prominent for patients in the s-CPR arm. Given the correlations mentioned above between primary endpoint success and use of those therapies, FDA observed that the rate of survival to discharge, either with or without good neurological function, was lower than at any other site. The differential was most prominent with regard to primary endpoint failure in s-CPR patients.

| | Site 06 | | Main Study | |
|--|------------------|--------------------|------------------|--------------------|
| | S-CPR (n=149) | ACD+ITD (n=169) | S-CPR (n=813) | ACD+ITD (n=840) |
| Survival to HD | 3 (2.0) | 18 (10.7) | 8 (9.9) | 104 (12.4) |
| Survival data not available | 2 | 0 | 6 | 2 |
| Survival to HD with MRS $\leq 3^2$ | 2 (1.3) | 12 (7.1) | 47 (5.9) | 75 (9.0) |
| <i>MRS scores at hospital discharge:</i> | | | | |
| 0 | 1 | 7 | 3 | 11 |
| 1 | 0 | 2 | 8 | 11 |
| 2 | 1 | 2 | 26 | 30 |
| 3 | 0 | 1 | 10 | 23 |
| 4 | 0 | 2 | 10 | 9 |
| 5 | 1 | 4 | 16 | 18 |
| 6 | 144 | 151 | 727 | 734 |
| Survived, MRS data not available | 0 | 0 | 7 | 2 |

The primary endpoint treatment effect ($\text{Rate}_{\text{ACD-ITD}} - \text{Rate}_{\text{s-CPR}}$) for the mITT population was 3%. Site 06 enrolled 18% and 20% of the mITT population control and treatment populations, respectively. The treatment effect at Site 06 (5.8%) was considerably greater than at any other site (range: -0.1%-4.4%). Thus despite its lower discharge rates, the odds ratio for achieving primary endpoint success (ACD-ITD vs. s-CPR) was particularly favorable at Site 06:



A study site poolability analysis provided by the sponsor showed no statistical evidence of a significant difference between sites in the primary endpoint. Nonetheless, Site 06's skewed utilization of beneficial adjuvant therapy, particularly among s-CPR patients, complicates the inferences to be drawn from the trial's results.

Additionally, as discussed above, Site 06 had both the highest number of major protocol deviations as well as the highest proportion of in-field major deviations among sites. FDA is concerned, therefore, that those deviations may have had downstream effects on patient conditions and management strategies, further confounding the estimate of the treatment effect.

Medication/Drug overdose

As noted previously, the sponsor elected to exclude medication/drug overdose patients from the mITT analysis population, even though the protocol specified their inclusion. 163 patients were adjudicated as overdose etiologies; a significantly higher proportion of ITT ACD-ITD patients were overdose etiology, as compared to the s-CPR.

**Table 6. Proportion of Subjects with Drug Overdose in ITT population
(By FDA)**

| S-CPR | ACD-ITD |
|-----------------|-----------------|
| 5.41% (65/1201) | 7.72% (98/1269) |

A *post hoc* sub-group analysis of the primary endpoint for overdose patients failed to demonstrate superiority for the treatment arm. Rather, the results suggested better outcomes in the control arm, though this was not statistically significant:

Table 7. Survival to Hospital Discharge with MRS \leq 3, Overdose Subjects, complete case analysis (By FDA)

| S-CPR (N=65) | ACD-ITD (N=98) |
|---------------------|-------------------------|
| 15.38% (10/65) | 9.28% (9/97), 1 missing |

To investigate the potential impact of these 163 excluded overdose subjects on the primary analysis results, FDA added them to the mITT cohort.

Table 8. Survival to Hospital Discharge with MRS ≤ 3, mITT plus 163 drug overdose subjects (Complete Case) (By FDA)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|--------------------------------|-------------------------------------|---------------------------------|-----------------|
| S-CPR vs. ACD-ITD [#] | 6.59% (57/865), 13 missing | 8.98% (84/935), 5 missing | 0.0652 |
| First 1400 subjects | 6.82% (47/689) | 9.46% (66/698) | 0.0776 |
| CHW | 6.59% (57/865)* | 8.98% (84/935)* | 0.0882** |

[#]: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Superiority was not met if the subjects identified as drug overdose are included in the mITT analysis.

Delayed CEC Adjudication

As noted previously, FDA identified 28 subjects who were included in the pivotal phase’s interim analyses by the DSMB of the mITT population, but were subsequently removed from the mITT analysis for the PMA submission. The sponsor explained that these 28 subjects were re-adjudicated by the CEC and removed for reasons such as metabolic and respiratory etiologies. 22 of the 28 patients were in the ACD-ITD arm.

Table 9. Survival to Hospital Discharge with MRS ≤ 3, Delayed Adjudication Subjects (By FDA)

| S-CPR | ACD-ITD |
|-----------|--------------|
| 50% (3/6) | 4.55% (1/22) |

To investigate the potential impact of these 28 subjects on the study conclusion, FDA added them to the mITT analysis population.

Table 10. Survival to Hospital Discharge with MRS ≤ 3, mITT plus 28 delayed adjudicated subjects (Complete Case) (By FDA)

| Approach | S-CPR | ACD-ITD | 2-sided p-value |
|---------------------|--------------------|--------------------|------------------------|
| S-CPR vs. ACD-ITD# | 6.20% (50/806) | 8.84% (76/860) | 0.0512 |
| First 1400 subjects | 6.48% (44/679) | 9.17% (65/709) | 0.0722 |
| CHW | 6.20% (50/806)* | 8.84% (76/860)* | 0.0642** |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Superiority was not met if these 28 late adjudicated subjects are included in both the mITT analysis and the as-treated analysis.

As-Treated Analyses

As noted previously, many subjects randomized to the ACD-ITD arm were treated with s-CPR alone, or only one part of the devices (either ACD or ITD), while some subjects randomized to the s-CPR arm were treated with ACD-ITD or one part of the device. Furthermore, although every subject in the mITT population received standard CPR for at least some initial period of resuscitation, FDA identified many ACD-ITD patients resuscitated without one or both of the devices who were considered primary endpoint successes. For circumstances such as that, FDA sees great value in evaluating device trial data on an “As Treated” basis in addition to the “Intent to Treat” (or modified Intent to Treat) basis. Accordingly, early on in its review of this PMA, FDA requested that the sponsor provide appropriate adjunctive As Treated analyses. The sponsor classified the subjects by the number of devices used:

Table 2. Number of Patients with Study Devices Used by Study Group, mITT (by the sponsor)

| Number of devices used | S-CPR (N=813) | ACD-ITD (N=842) |
|-------------------------------|----------------------|------------------------|
| 0 | 803 | 28 |
| 1 (1 ITD or 1 ACD) | 5 | 32 |
| 2 (1 ITD and 1 ACD) | 5 | 782 |

The sponsor used three methods to perform the as-treated analysis. .

Method 1

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with a least "1" device, either ACD, ITD, or both (n = 782+32 = 814)

Method 2

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with both ACD and ITD devices (n = 782)

Method 3

- All Subjects, regardless of randomization assignment, re-classified as having received s-CPR with "0" devices (n=803+28=831) or having received ACD-ITD with "2" devices (n782+5=787).

Table 11. Survival to Hospital Discharge with MRS ≤ 3, As-Treated Analysis (Complete Case) (By the sponsor)

| Method# | s-CPR | ACD-ITD | 2-sided p-value |
|----------------|------------------|------------------|------------------------|
| Method 1: | 5.9% (47/790) | 8.3% (67/811) | 0.080 |
| Method 2: | 5.9% (47/790) | 8.1% (63/779) | 0.113 |
| Method 3: | 6.7% (55/817) | 8.0% (63/784) | 0.339 |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

In all three of the sponsor’s As-Treated analyses, the treatment arm did not demonstrate statistical superiority.

FDA defined a fourth As-Treated method

Method 4

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- all ACD-ITD subjects, irrespective of devices actually used (n=782+32+28=842).

The as-treated methods were analyzed using alpha control approaches previously defined

(First 1400 and CHW). The sponsor analyzed the first three methods; FDA analyzed four as-treated methods.

Table 12. Survival to Hospital Discharge with MRS \leq 3, As-Treated Analysis (Complete Case) (By FDA)

| Approach | Method | S-CPR | ACD-ITD | 2-sided p-value |
|---------------------|----------|---------------------|---------------------|-----------------|
| First 1400 subjects | Method 1 | 6.07% (41/675) | 8.50% (58/682) | 0.0949 |
| | Method 2 | 6.07% (41/675) | 8.24% (54/655) | 0.1364 |
| | Method 3 | 6.74% (47/697) | 8.19% (54/659) | 0.3518 |
| | Method 4 | 6.07% (41/675) | 9.09% (64/704) | 0.0419 |
| CHW | Method 1 | 5.95% (47/790) * | 8.26% (67/811) * | 0.1060** |
| | Method 2 | 5.95% (47/790) * | 8.09% (63/779) * | 0.1480** |
| | Method 3 | 6.73% (55/817) * | 8.04% (63/784) * | 0.4250** |
| | Method 4 | 5.95% (47/790) * | 8.95% (75/838) * | 0.0342** |

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

In FDA’s As-Treated analyses addressing alpha inflation, the treatment arm did not demonstrate statistical superiority in the first three methods. In FDA’s method 4, which compared the ACD-ITD “mITT” population to a s-CPR “no device” population, for complete cases the nominal p-value was less than the two-sided alpha of 0.049.

FDA also applied the 4 methods to the mITT populations augmented with the patients excluded on the basis of medication/drug overdose and delayed CEC adjudications (see above). Statistical superiority was not demonstrated for these populations under any of the 4 As-Treated method scenarios (Appendix 3).

To investigate why the first three as-treated analyses lead to a more conservative conclusion than the sponsor’s primary analysis (i.e., superiority was not concluded), FDA tabulated the primary endpoint rate by number of devices used in each treatment arm:

Table 13. Survival to Hospital Discharge with MRS \leq 3 (Complete Case) (By the FDA)

| Number of Devices Used | s-CPR | ACD-ITD |
|-------------------------------|-----------------------------|----------------------------|
| 0 | 5.95% (47/790), missing: 13 | 29.63% (8/27), missing: 1 |
| 1 | 0% (0/5) | 12.50% (4/32) |
| 2 | 0% (0/5) | 8.09% (63/779), missing: 3 |

It is noteworthy that the rate of primary endpoint success is substantially higher among ACD-ITD subjects who never received device therapy (partial or full) than among any other stratum. FDA believes this fact may explain why the mITT analysis provides more promising results in favor of the ACD-ITD arm than do the as-treated analyses.

From a statistical perspective, the dramatic difference in endpoint success between two groups of subjects, neither of which received any device-based therapy, is difficult to reconcile. This finding raises concerns for FDA that the mITT analysis is unreliable. The sponsor explains these results by stating that standard CPR is an obligatory first step to proper use of ACD-ITD and that the high rate of success reflects a self-selected group of ACD-ITD patients who rapidly developed ROSC (i.e., before device use). Nonetheless, instances of ACD-ITD (treatment arm mITT) success in the setting of prolonged standard CPR without complete system use were identified, i.e., randomization error/other improper use of the device.

Effect of unavailable endpoint data

Methods to handle missing data:

Please note that the analysis population only indicates which subjects should be included in the analysis. However, it does not indicate how to handle the missing data. Usually missing data are handled through three different methods within an analysis population, depending upon the mechanism underlying the missing data (see Appendix 4):

- 1) complete-case analysis which excludes the subjects with missing data;
- 2) Multiple imputation method which imputes the missing data via a statistical model;
- 3) Sensitivity analysis (to be more specific for this study, tipping point analysis) which evaluates the impact of missing data on the study conclusion under different scenario.

In this study there were 17 subjects without mRS values in the mITT population. The protocol did not specify a mechanism for imputation of the missing data. In the data analysis, most analyses were complete-case analyses. In addition, the sponsor performed multiple imputations for the primary endpoint in the mITT population. FDA performed tipping point analyses as well as the best-case scenario analyses for both mITT and as-treated analysis populations.

As stated above, 17 mITT patients had unavailable mRS and/or discharge status data for determining the primary endpoint (Appendix 5). The rate of undocumented data was three times greater in the control arm (1.6%) than in the treatment arm (0.5%). FDA accepts the sponsor’s explanation (lack of patient consent) for the “missing” data in these 17 patients. However, the sponsor did not provide a completely satisfactory explanation for why more control arm patients declined the consent than did test arm patients.

The protocol did not specify a mechanism for imputation of missing data. FDA performed a sensitivity analysis on the 4 As-Treated analyses above, using a best-case scenario. Under the best-case scenario, all missing values in the ACD-ITD arm are imputed as discharged with mRS ≤ 3 while all the missing values in the s-CPR arm are imputed as mRS > 3.

Table 14. Survival to Hospital Discharge with MRS ≤ 3, Best Case Analysis for as-treated population (By FDA)

| Approach | Method | S-CPR | ACD-ITD | 2-sided p-value |
|---------------------|----------|-----------------|-----------------|-----------------|
| First 1400 subjects | Method 1 | 5.99% (41/684) | 8.77% (60/684) | 0.0623 |
| | Method 2 | 5.99% (41/684) | 8.52% (56/657) | 0.0912 |
| | Method 3 | 6.65% (47/707) | 8.47% (56/661) | 0.2191 |
| | Method 4 | 5.99% (41/684) | 9.48% (67/707) | 0.0162 |
| CHW | Method 1 | 5.85% (47/803)* | 8.60% (70/814)* | 0.0500** |
| | Method 2 | 5.85% (47/803)* | 8.44% (66/782)* | 0.0712** |
| | Method 3 | 6.62% (55/831)* | 8.39% (66/787)* | 0.2442** |
| | Method 4 | 5.85% (47/803)* | 9.38% (79/842)* | 0.0116** |

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

**: two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

In the first three As-Treated (best case scenario) analyses, the treatment arm did not demonstrate statistical superiority. Only Method 4 (best case scenario), which compared the ACD-ITD “mITT” population to a s-CPR “no device” population yielded a nominal p-value less than an alpha of 0.049.

FDA performed a tipping point analysis to evaluate the robustness of the conclusion under method 4. The tipping point analysis replaced missing data with values to determine the point at which the study conclusion becomes altered. As can be seen FDA found the superiority conclusion in method 4 to be sensitive to the missing data and very sensitive particularly when considering alpha inflation.

In the tipping point analysis figures, the x-axis represents the number of primary successes ($mRS \leq 3$) in the missing cohort of the ACD-ITD arm, and the y-axis represents the number of primary successes ($mRS \leq 3$) in the missing cohort of the s-CPR arm. The red blocks represent the scenario when the two-sided p-value is greater than or equal to 0.049 (which was specified after the s-ITD arm was dropped), the yellow blocks represent the scenario when the two-sided p-value is greater than or equal to 0.022 but less than 0.049, and the light blue blocks represent the scenario when the two-sided p-value is less than 0.022.

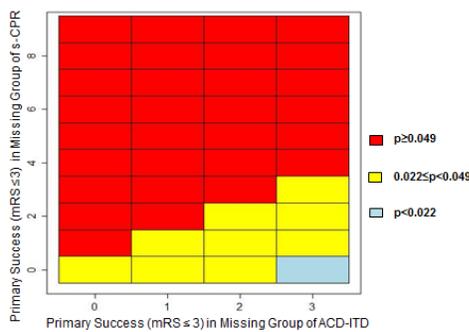


Figure 6.2.1 Tipping Point Analysis for As-Treated Analysis Method 4 First 1400 mITT subjects

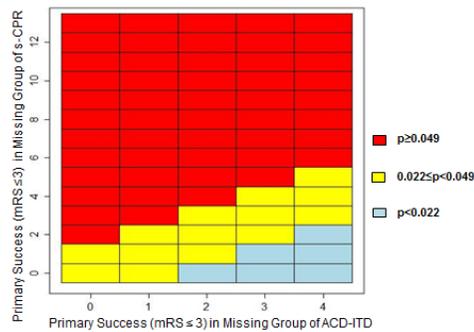


Figure 6.2.2 Tipping Point Analysis for As-Treated Analysis Method 4 CHW approach

FDA also performed a tipping point analysis on the mITT population, and the results were similar:



Figure 6.2.3 Tipping Point Analysis for mITT subjects – First 1400

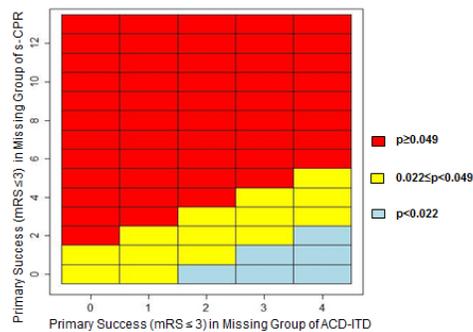


Figure 6.2.4 Tipping Point Analysis for mITT subjects – CHW approach

The nominal p-values were less than an alpha of 0.049 in Method 4, but the analysis was found to be sensitive to the missing data and very sensitive particularly when considering alpha inflation.

FDA notes a trend for clinical effectiveness of the ACD-ITD device, as demonstrated by the point estimates of success in the tables above. FDA will be seeking the panel’s interpretation of this apparent effectiveness signal in the context of FDA’s study conduct concerns.

Secondary Endpoints

Powered Safety

Secondary Safety Endpoint

The rate of pre-specified major adverse events in the treatment arm was found to be non-inferior ($p < 0.0001$) within the pre-specified 5% non-inferiority margin.

Table 15: Final outcome for the secondary safety endpoint: major adverse event (mITT) (By FDA)

| | S-CPR (N=813) | ACD-ITD (N=842) | ACD-ITD – S-CPR (95.6% C.I) |
|---------|----------------------|------------------------|------------------------------------|
| Pivotal | 93.8% (763/813) | 92.9% (782/842) | -0.98% [-3.5%, 1.5%] |

Note: The upper bound of 95.6% CI should be compared with the non-inferiority margin of 5%

The rate for the adverse event of pulmonary edema was statistically significantly greater in ACD-ITD patients. One quarter of all patients with “pulmonary edema” died in the field and thus were diagnosed by EMS personnel on clinical grounds alone.

Table 10.1: Secondary Safety Endpoint Analysis: Major Adverse Events through Hospital Discharge, mITT¹

| Event | S-CPR (N= 813 subjects) | ACD+ITD (N= 842 subjects) | p value |
|---|----------------------------|------------------------------|---------|
| Subjects with ≥1 Major Adverse Event through hospital discharge (Secondary Safety Endpoint ³) | 763 (93.8%) | 782 (92.9%) | 0.432 |
| Death, through hospital discharge | 729 (89.7) | 735 (87.3) | 0.144 |
| Re-arrest | 161 (19.8) | 185 (22.0) | 0.304 |
| CVA/cerebral bleeding | 3 (0.4) | 2 (0.2) | 0.682 |
| Internal organ injury | 0 | 1 (0.1) | 1.000 |
| Bleeding requiring transfusion or surgical intervention | 3 (0.4) | 7 (0.8) | 0.343 |
| Seizure | 13 (1.6) | 11 (1.3) | 0.684 |
| Rib/Sternal fracture | 14 (1.7) | 11 (1.3) | 0.549 |
| Pulmonary edema ³ | 62 (7.6) | 94 (11.2) | 0.015 |

¹Numbers shown are subjects with at least one report of the listed adverse event types. If multiple events of same type were reported, the event is only counted once per subject. Reports of deaths, re-arrest, seizure, and pulmonary edema in the field (e.g., pre-hospital) are also shown. All other adverse event types were assessed based on review of medical records for subjects transported to a hospital. There were no Major Adverse Events associated with device malfunctions, defects, or failures.

The rate of pulmonary edema in the ACD-ITD arm (11.2%) was higher than the rate observed in the s-ITD arm (7.3%) or in the treatment arm of ROC PRIMED (5.8%), both of which were clinically comparable to their trials' respective control arm rates of pulmonary edema

The association of pulmonary edema with use of the ITD has been previously described. We acknowledge the sponsor's paradoxical post hoc finding that pulmonary edema was associated with improved clinical outcome. FDA does not find evidence from the current dataset to suggest that the adverse event results in quantifiable injury to cardiac arrest patients.

Device Failures

Table 22 ResQPOD and ResQPump Device Failures Among all Subjects Provisionally Enrolled to ACD+ITD or S-CPR +ITD in either the Run-in or Pivotal Study Phase (Numbers shown are reported adverse events due to device failure)

| | Run-in Phase | Pivotal Phase | Total |
|--|---------------|-----------------|-----------------|
| <i>ResQPOD device failure¹:</i> | | | |
| timing light | 14 | 102 | 116 |
| inadequate connection of ETCO ₂ adaptor to device | 1 | 0 | 1 |
| male adaptor of BVM broke off, lodged within device | 0 | 1 | 1 |
| difficult ventilation using device, unspecified | 0 | 1 | 1 |
| ResQPOD Failure Rate, overall² | 15/200 (7.5%) | 104/1497 (6.7%) | 119/1697 (7.0%) |
| ResQPOD Failure adversely affecting patient care | 0 | 0 | 0 |
| <i>ResQPump device failure¹:</i> | | | |
| force gauge | 1 | 2 | 3 |
| metronome | 0 | 13 | 13 |
| suction cup detachment | 0 | 1 | 1 |
| ResQPump Failure Rate, overall² | 1/134 (0.7%) | 16/1269 (1.3%) | 17/1403 (1.2%) |
| ResQPump failure adversely affecting patient care | 0 | 0 | 0 |

¹See text for detailed description.

²ResQPOD failure rate defined as number of subjects with reported device failure divided by total number of subjects who were randomized to S-CPR +ITD or to ACD+ITD. ResQPump failure rate defined as number of subjects with reported device failure divided by total number of subjects randomized to ACD+ITD. "Failure with discontinued device use" refers to number of subjects with device failure type that necessitated the discontinuation of further use of the device.

The number and type of device failures do not raise any particular concerns for FDA.

Effectiveness

The Secondary Effectiveness hypothesis was that CASI in treatment arm patients at 90 days and 1 year would be superior to the scores of control arm patients.

The trial failed to demonstrate superiority for System patients on the basis of CASI scores at either 90 days or one year. (The secondary endpoint involved hierarchical testing; thus, no test for superiority was performed on the one-year data.). There were substantial amounts of missing CASI data.

**Table 16: The secondary effectiveness endpoints: mean \pm std.
(No imputation, by the sponsor), 2-sided alpha = 0.05**

| | S-CPR | ACD-ITD | 2-sided P-value |
|------------------------|-----------------------------|-----------------------------|-----------------|
| CASI at 90 days | 93.76 \pm 6.78 (n=38) | 91.08 \pm 13.18 (n=49) | 0.257 |
| CASI at 1 year | 93.73 \pm 11.77 (n=30) | 94.68 \pm 4.40 (n=41) | |

Table 3.1: ResQTrial- CASI Score Distribution [mITT]

| | 90 Days ^{1,2} | | One Year ^{1,3} | |
|---|------------------------|-------------------|-------------------------|-------------------|
| | S-CPR (n=58) | ACD+ITD (n=87) | S-CPR (n=48) | ACD+ITD (n=74) |
| CASI data available (% of survivors) | 38 (65.5) | 49 (56.3) | 30 (62.5) | 41 (55.4) |
| <i>Distribution of CASI scores:</i> | | | | |
| 90-100 (% of subjects with CASI data available) | 31 (81.6) | 39 (79.6) | 26 (86.7) | 35 (85.4) |
| 80-89 | 4 (10.5) | 6 (12.2) | 2 (6.7) | 6 (14.6) |
| 70-79 | 3 (7.9) | 3 (6.1) | 0 (0) | 0 (0) |
| 60-69 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 50-59 | 0 (0) | 0 (0) | 1 (3.3) | 0 (0) |
| 40-49 | 0 (0) | 0 (0) | 1 (3.3) | 0 (0) |
| 30-39 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 20-29 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 0-19 | 0 (0) | 1 (2.0) | 0 (0) | 0 (0) |
| Alive, but CASI data not available (% of survivors) | 20 | 38 | 18 | 33 |
| Subjects with CASI data at 90 day & 1 year | -- | -- | 28 | 35 |
| <i>CASI at 1 year compared with 90 days (% of subjects with data at both 90 days and 1 year):</i> | | | | |
| improved score | | | 15 (53.6) | 22 (62.9) |
| no change in score | | | 3 (10.7) | 3 (8.6) |
| degraded score | | | 10 (35.7) | 10 (28.6) |

¹ N shown is number of survivors at 90 days and 1 year, respectively.

CASI data from the s-ITD arm, though limited, were consistent with the treatment-control comparative findings.

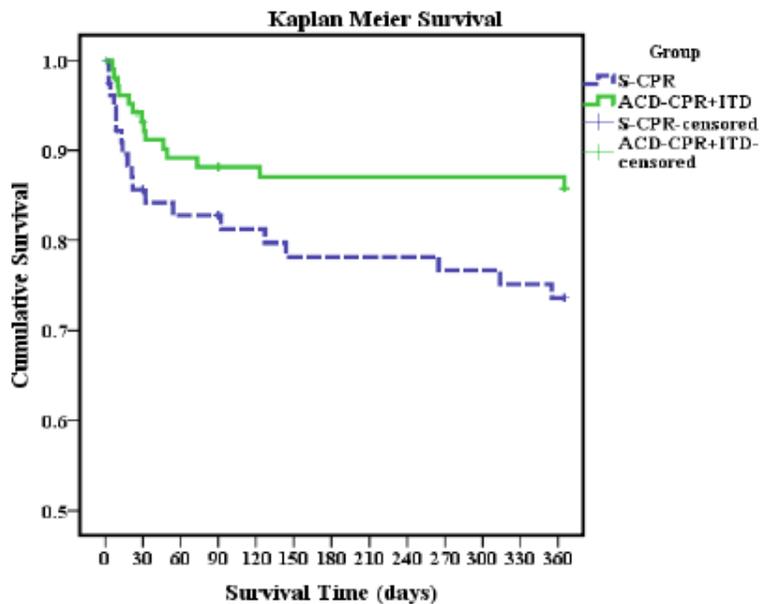
| | S-CPR (N=813) | ACD+ITD (N=840) | S-CPR+ITD (n=150) |
|--|-------------------------|-------------------------|----------------------|
| Survived to 90 days | 58 (7.3) | 87 (10.5) | 6 (4.0) |
| Not available | 15 | 9 | - |
| CASI (mean score +/- SD, survivors only) | 93.76 ± 6.78 (n=38) | 91.08 ± 13.18 (n=49) | 89.17 ± 9.75 |
| Survived to one year | 48 (6.0) | 74 (9.0) | 5 (3.3) |
| Not available | 19 | 20 | |
| CASI (mean score +/- SD, survivors) | 93.73 ± 11.77 (n=30) | 94.68 ± 4.40 (n=41) | 89.75 ± 11.53 |

The difference between s-CPR and ACD-ITD in CASI scores was not significant at 90 days or 1 year.

Secondary Endpoints without pre-specified hypotheses

Although at 90 days and beyond, there was neither a statistically significant nor clinically meaningful difference between arms in neurological function as measured by CASI, survival (irrespective of neurological status) out to one year among discharged patients (or patients alive at 30 days) was higher in the ACD-ITD arm.

Figure C: Kaplan Meier Survival [all mITT subjects discharged alive or alive at 30 days]
[source= Listing 262] Unadjusted P= 0.048, Log Rank (Mantel-Cox) test of equality of survival distributions for the different levels of Group.



FDA agrees with the sponsor's analyses demonstrating:

- longer-term survival, in both arms, tended to be associated with mRS ≤ 3 as compared to mRS > 3 ;
- the comparability of longer-term CPC, OPC, and DRS scores, showing minimal neurological deficits among longer-term survivors.

Table 31 90 Day Follow-Up and Neurologic Assessments, mITT¹

| | S-CPR (n=813) | ACD+ITD (n=840) |
|---|------------------------|--------------------------|
| Survival to 90 days | 58 (7.3) | 87 (10.5) |
| Not available | 15 | 9 |
| Reported re-arrest since discharge | 1 | 1 |
| Reported devices implanted since hospital discharge | 0 | 1 |
| ICD | 0 | 1 |
| Pacemaker | 0 | 0 |
| CPC ² | | |
| 1 | 42 | 66 |
| 2 | 5 | 6 |
| 3 | 3 | 3 |
| 4 | 0 | 2 |
| CPC ≤ 2 at 90 days | 47 (5.8) | 72 (8.7) |
| OPC ³ | | |
| 1 | 36 | 54 |
| 2 | 8 | 15 |
| 3 | 6 | 6 |
| 4 | 0 | 2 |
| Not available | 8 | 10 |
| Beck Depression Inventory (mean score ± SD) | 4.80 ± 3.91 (n=44) | 6.51 ± 6.77 (n=65) |
| Mayo Portland Adaptability Inventory (mean score ± SD) | 13.23 ± 22.51 (n=48) | 13.94 ± 24.39 (n=67) |
| CASI (mean score ± SD, among survivors) | 93.76 ± 6.78 (n=38) | 91.08 ± 13.18 (n=49) |
| CASI, secondary endpoint ³ | 69.86 ± 41.68 | 74.38 ± 37.48 |
| HUI3 (mean score ± SD) | 11.86 ± 3.89 (n=44) | 12.35 ± 5.98 (n=66) |
| Trail Making A (mean score ± SD) | 42.53 ± 27.03 (n=36) | 49.80 ± 34.12 (n=51) |
| Trail Making B (mean score ± SD) | 83.09 ± 40.05 (n=34) | 108.62 ± 50.46 (n=47) |
| DRS ⁴ (mean score ± SD) | 1.91 ± 3.41 (n=47) | 2.58 ± 5.22 (n=74) |
| None | 25 | 32 |
| Mild | 7 | 12 |
| Partial | 8 | 17 |
| Moderate | 2 | 7 |
| Moderately severe | 4 | 3 |
| Extremely severe | 1 | 1 |
| Extreme vegetative | 0 | 2 |

Table 32 One Year Follow-Up and Neurologic Assessments, mITT¹

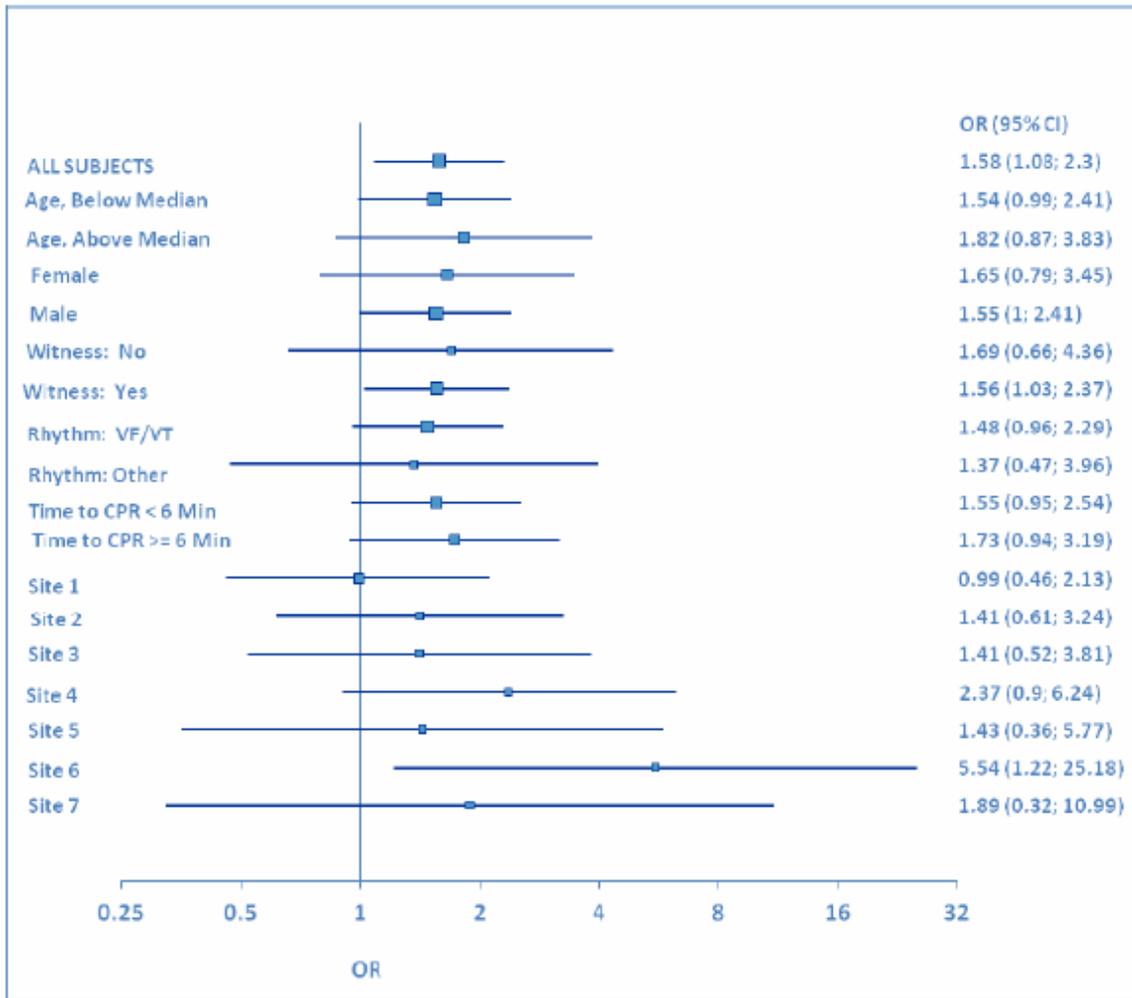
| | S-CPR (n=813) | ACD+ITD (n=840) |
|---|--------------------------|----------------------------|
| Survival to 1 year | 48 (6.0) | 74 (9.0) |
| Not available | 19 | 20 |
| Reported re-arrest since discharge | 3 | 0 |
| Reported devices implanted since hospital discharge | 1 | 2 |
| ICD | 1 | 1 |
| Pacemaker | 0 | 1 |
| CPC ² | | |
| 1 | 38 | 56 |
| 2 | 5 | 6 |
| 3 | 2 | 1 |
| 4 | 0 | 2 |
| Not available | 3 | 9 |
| CPC ≤ 2 at one year | 43 (5.4) | 62 (7.6) |
| OPC ² | | |
| 1 | 34 | 48 |
| 2 | 8 | 14 |
| 3 | 3 | 1 |
| 4 | 0 | 2 |
| Not available | 3 | 9 |
| Beck Depression Inventory (mean score ± SD) | 5.23 ± 6.29 (n=35) | 5.46 ± 5.93 (n=57) |
| CASI (mean score ± SD, among survivors) | 93.73 ± 11.77 (n=30) | 94.68 ± 4.40 (n=41) |
| CASI, secondary endpoint ³ | 57.39 ± 47.04 | 71.89 ± 41.04 |
| HUI 3 (mean score ± SD) | 12.49 ± 4.45 (n=37) | 12.10 ± 6.00 (n=60) |
| Trail making A (mean score ± SD) | 49.56 ± 43.37 (n=32) | 47.10 ± 27.26 (n=39) |
| Trail making score B (mean score ± SD) | 87.48 ± 43.12 (n=27) | 100.54 ± 64.47 (n=35) |
| Quality of Life (mean score ± SD) | 2.02 ± 0.79 (n=41) | 2.09 ± 0.99 (n=64) |
| DRS ⁴ (mean score ± SD) | 1.39 ± 3.12 (n=41) | 2.19 ± 5.68 (n=63) |
| None | 27 | 35 |
| Mild | 4 | 6 |
| Partial | 5 | 15 |
| Moderate | 3 | 4 |
| Moderately severe | 1 | 0 |
| Extremely severe | 1 | 0 |
| Extreme vegetative | 0 | 3 |

Additional Analyses

Sub-Group Analyses

The sponsor explored the performance of ACD-ITD vs. s-CPR across pre-specified subgroups in terms of the primary endpoint. In general, the direction of the treatment effect appeared consistent with the primary endpoint, except site 1 in which the odds ratio is in favor of s-CPR. The Figure below presents the sponsor’s analysis results.

Effect of Age, Gender, Witnessed Status, Initial Rhythm, Time to CPR, and Study Site on Estimated Odds Ratio (OR) for Primary Endpoint (ACD-ITD vs. SCPR) in mITT Population



Estimated odds ratios exceeded 1.00 for subgroups based on age, gender, witnessed status, time to start of CPR, and at 6 of 7 total study sites. VF/VT- ventricular fibrillation and pulseless ventricular tachycardia; CPR cardiopulmonary resuscitation. Median age was 67 years ((IQR 56-79).

Potential implications of Site 06’s performance were discussed previously.

Presenting rhythm of VF/VT appeared to be associated with more favorable outcomes. As FDA noted previously, adjudication led to mITT exclusion of substantially more control arm VF/VT endpoint successes treatment arm.

Gender-specific Results

Primary Effectiveness

The proportion of male subjects in each arm of the trial was the same (66%, mITT). The trial identified improved outcomes in men compared to women independent of therapy; the treatment effect in men was slightly more pronounced than in women. The sub-group

analysis was not powered to allow for statistical testing.

Table 37 MRS at Hospital Discharge by Gender, mITT¹

| | S-CPR | ACD+ITD | TOTAL |
|---|-----------|-----------|-----------|
| Males, total | 539 | 558 | 1097 |
| <i>MRS, males</i> | | | |
| 0 | 2 | 4 | 6 |
| 1 | 6 | 8 | 14 |
| 2 | 19 | 26 | 45 |
| 3 | 8 | 17 | 25 |
| 4 | 5 | 7 | 12 |
| 5 | 9 | 11 | 20 |
| 6 | 481 | 483 | 964 |
| Survival at discharge not available | 3 | 1 | 4 |
| Survived, MRS not available | 6 | 1 | 7 |
| Hospital discharge with MRS ≤ 3 (Primary Endpoint) | 35 (6.6%) | 55 (9.9%) | 90 (8.3%) |
| Females, total | 274 | 282 | 556 |
| <i>MRS, females</i> | | | |
| 0 | 1 | 7 | 8 |
| 1 | 2 | 3 | 5 |
| 2 | 7 | 4 | 11 |
| 3 | 2 | 6 | 8 |
| 4 | 5 | 2 | 7 |
| 5 | 7 | 7 | 14 |
| 6 | 246 | 251 | 497 |
| Survival at discharge not available | 3 | 1 | 4 |
| Survived, MRS not available | 1 | 1 | 2 |
| Hospital discharge with MRS ≤ 3 (Primary Endpoint) | 12 (4.4%) | 20 (7.1%) | 32 (5.8%) |

[Source: Appendix 13c. Listing 178 (males); Listing 179 (females); Listing 180- Odds ratio and confidence interval]

¹ Data shown are number of subjects. Comparisons between groups were done in stratified 2x2 tables. There was no evidence of a difference in odds ratio (OR) between genders (p=1.000). A Mantel-Haenszel analysis was performed. There was no difference in the OR between genders: OR= 1.579 (95% CI 1.081, 2.306).

FDA does not believe the cumulative data indicate a clinically important difference in System effectiveness when used in female patients.

Secondary Safety

Female patients experienced the pulmonary edema and pneumothorax adverse events more frequently than male patients, irrespective of randomization arm. Event rates were clinically similar between ACD-ITD and s-CPR gender sub-groups.

| | S-CPR | | | ACD+ITD | | |
|---|-----------------|-------------------|------------------|-----------------|-------------------|------------------|
| | Male (n=539) | Female (n=274) | Total (N=813) | Male (n=558) | Female (n=282) | Total (N=840) |
| Subjects with ≥1 Major Adverse Event through hospital discharge | 507 (94.1) | 259 (94.5) | 766 (94.2) | 518 (92.8) | 269 (95.4) | 787 (93.7) |
| Death, total | 482 (89.4) | 247 (90.1) | 729 (89.7) | 483 (86.6) | 251 (89.0) | 734 (87.4) |
| death, pre-hospital | 230 (42.7) | 105 (38.3) | 335 (41.2) | 230 (41.2) | 126 (44.7) | 356 (42.4) |
| Re-arrest, total | 106 (19.7) | 55 (20.1) | 161 (19.8) | 120 (21.5) | 64 (22.7) | 184 (21.9) |
| Re-arrest, pre-hospital | 90 (16.7) | 41 (15.0) | 131 (16.1) | 104 (18.6) | 48 (17.0) | 152 (18.1) |
| CVA/cerebral bleeding | 1 (0.2) | 2 (0.7) | 3 (0.4) | 1 (0.2) | 1 (0.4) | 2 (0.2) |
| Internal organ injury | 0 | 0 | 0 | 0 | 1 (0.4) | 1 (0.1) |
| Hemothorax | 0 | 1 (0.4) | 1 (0.1) | 2 (0.4) | 0 | 2 (0.2) |
| Bleeding requiring intervention | 1 (0.2) | 2 (0.7) | 3 (0.4) | 6 (1.1) | 1 (0.4) | 7 (0.8) |
| Cardiac tamponade | 2 (0.4) | 1 (0.4) | 3 (0.4) | 1 (0.2) | 1 (0.4) | 2 (0.2) |
| Aspiration | 3 (0.6) | 4 (1.5) | 7 (0.9) | 5 (0.9) | 3 (1.1) | 8 (1.0) |
| Pneumothorax | 0 | 7 (2.6) | 7 (0.9) | 4 (0.7) | 6 (2.1) | 10 (1.2) |
| Seizure, total | 6 (1.1) | 7 (2.6) | 13 (1.6) | 9 (1.6) | 2 (0.7) | 11 (1.3) |
| Seizure, pre-hospital | 1 (0.2) | 0 | 1 (0.1) | 0 | 0 | - |
| Rib/Sternal fracture | 5 (0.9) | 9 (3.3) | 14 (1.7) | 6 (1.1) | 5 (1.8) | 11 (1.3) |
| Pulmonary edema, total | 36 (6.7) | 26 (9.5) | 62 (7.6) | 57 (10.2) | 36 (12.8) | 93 (11.1) |
| Pulmonary edema, pre-Hospital | 13 (2.4) | 9 (3.3) | 22 (2.7) | 20 (3.6) | 9 (3.2) | 29 (3.5) |

FDA did not identify any gender-specific safety signals with device use that would substantially alter the benefit-risk profile for male or female patients. The higher adverse event rates observed in female ACD-ITD patients are likely not specifically device-related.

Airway-specific Primary Effectiveness Results

2% of the mITT population appears to have had the airway managed with a facemask only (i.e., not with an endotracheal tube, combi-tube, or laryngeal-mask airway)

Table 38 MRS Results at Hospital Discharge by Arrest Surroundings, mITT

| | S-CPR | ACD+ITD | Total | P value |
|---|-------|---------|-------|---------|
| Subjects in whom secured airway was <u>not</u> obtained (e.g., with ETT, combitube, LMA) ⁵ | 49 | 43 | 92 | |
| MRS: | | | | |
| 0 | 1 | 4 | 5 | |
| 1 | 2 | 3 | 5 | |
| 2 | 10 | 6 | 16 | |
| 3 | 3 | 6 | 9 | |
| 4 | 2 | 0 | 2 | |
| 5 | 0 | 2 | 2 | |
| 6 | 26 | 22 | 48 | |
| Survived, MRS not available | 5 | 0 | 5 | |
| Hospital discharge with MRS ≤ 3 (Primary Endpoint) | 16 | 19 | 35 | 0.516 |

The ITD is intended to be utilized only with a reasonably secured airway. The primary endpoint success rate, 44%, among treatment arm patients without a secured airway are therefore notable.

6.3 FDA Considerations and Conclusions

The data presented for the mITT primary endpoint appear to demonstrate a clinically significant positive effect on survival to discharge with good neurological function [mRS \leq 3]. Among patients that do survive, the incremental neurological benefit associated with device use may diminish at longer follow-up.

The robustness of the mITT primary endpoint finding is unclear to FDA. Multiple adjunctive analyses have been performed and a small survival benefit is suggested for both the mITT and adjunctive analyses for the ACD-ITD arm. However, interpretation of findings for all analyses is clouded by statistical and trial conduct issues. Taking into account the strengths and limitations of the clinical trial, the panel will be asked to provide an assessment of the totality of the data and provide a risk/benefit analysis for the ACD-ITD system.

7 Post Approval Study

A post-approval study for the ResQCPR™ System in the out-of-hospital cardiac arrest patient population is discussed below. We are seeking Panel input regarding the practicality and/or benefit of a post-approval study for the ResQCPR System should the device be granted marketing approval:

Post-market Concern 1:

Evaluation of longer-term performance

Long-term evaluation of the device is not necessary since the device is designed for emergency use to resuscitate patients who have suffered a cardiac arrest. Once the patient has a return of spontaneous circulation (e.g. palpable pulse) during the resuscitation effort, the device is no longer intended to be used.

Post-market Concern 2:

Evaluation of the effectiveness of training program

A poolability analysis showed no statistically significant difference between sites in the primary endpoint. Additionally, for a given site the s-CPR and ACD-ITD mITT exclusion rates were similar (suggesting similar intra-site execution of the field protocol for both study arms). FDA believes the training protocol can be effective in assuring the proper use of the ResQCPR™ System. Since training in the proper use of the ResQCPR™ System is essential for both safety and effectiveness, a rigorous **training program will be required as part of the labeling** for the device and certification per person as opposed to per site will be considered.

FDA would like to ask the Panel whether a post-approval study may be useful in evaluating the effectiveness of the training protocol.

Post-market Concern 3:

Evaluation of performance on specific sub-groups of intended population

The effect estimate for survival to hospital discharge with an MRS <3 comparing ACD+ITD versus S-CPR in men (Odd Ratio (OR) =1.55, 95% confidence interval (CI): 1.00, 2.41) was of similar magnitude to that in women (OR=1.65, 95% CI: 0.79-3.45). Twelve (12) out of 274 (4.4%) female patients in the S-CPR arm and 20 out of 282(7.4%) in the ACD-ITD arm survived to hospital discharge with mRS≤3. **PAS evaluation of device performance in sub-groups is not recommended.**

Post-market Concern 4:

Monitoring for adverse events (including rare adverse events)

The pivotal study evaluated 12 adverse events. The overall rate of major adverse events was not significantly different between groups except for pulmonary edema. The treatment arm had higher risk of pulmonary edema (7.6% vs. 11.1%, P=0.018), which was statistically significant. Pulmonary edema is a manifestation of heart failure and an anticipated clinical consequence of cardiac arrest and CPR in general. The presence of pulmonary edema was not associated with worse outcomes in this trial. **A PAS to evaluate adverse events is not recommended.**

Post-market Concern 5:

Monitoring for performance of the device in practice

The sponsor intends to track outcomes in patients treated with the ResQCPR system for cardiac arrest in Emergency Medical Services (EMS) through the Cardiac Arrest Registry to Enhance Survival (CARES) and in-hospital cardiac arrest through the Get With The Guidelines®-Resuscitation registry, formerly known as National Registry of CPR (NRCPR). As is known, data collection through registries can be limiting.

FDA would like to ask the Panel whether a post-approval study, via the collection of outcomes data through the CARES and NRCPR registries may be useful in evaluating the effectiveness of the device, for example when used in different communities.

Appendix 1

Primary Endpoint Hypothesis (superiority)

s-CPR vs. ACD-ITD

H₀: Survival to hospital discharge with a good neurologic outcome for patients receiving ACD-ITD is equal to or less than that for patients receiving s-CPR.

$$\text{Rate}_{\text{ACD-ITD}} \leq \text{Rate}_{\text{s-CPR}}$$

H₁: Survival to hospital discharge with a good neurologic outcome for patients receiving ACD-ITD is greater than that for patients receiving s-CPR.

$$\text{Rate}_{\text{ACD-ITD}} > \text{Rate}_{\text{s-CPR}}$$

s-CPR vs. s-ITD

H₀: Survival to hospital discharge with a good neurologic outcome for patients receiving s-ITD is equal to or less than that for patients receiving s-CPR.

$$\text{Rate}_{\text{s-ITD}} \leq \text{Rate}_{\text{s-CPR}}$$

H₁: Survival to hospital discharge with a good neurologic outcome for patients receiving s-ITD is greater than that for patients receiving s-CPR.

$$\text{Rate}_{\text{s-ITD}} > \text{Rate}_{\text{s-CPR}}$$

Fisher's exact test was specified for the primary hypothesis test.

Secondary Safety Endpoint Hypothesis (non-inferiority)

s-CPR vs. ACD-ITD

H₀: The major adverse event rate for patients receiving ACD-ITD is inferior to that for patients receiving s-CPR.

$$\text{AE}_{\text{ACD-ITD}} \geq \text{AE}_{\text{s-CPR}} + 5\%$$

H₁: The major adverse event rate for patients receiving ACD-ITD is non-inferior to that for patients receiving s-CPR.

$$\text{AE}_{\text{ACD-ITD}} < \text{AE}_{\text{s-CPR}} + 5\%$$

s-CPR vs. s-ITD (*This analysis was subsequently abandoned due to dropping of the s-ITD arm from the study*)

H₀: The major adverse event rate for patients receiving s-ITD is inferior to that for

patients receiving s-CPR.

$$AE_{s-ITD} \geq AE_{s-CPR} + 5\%$$

H₁: The major adverse event rate for patients receiving s-ITD is non-inferior to that for patients receiving s-CPR.

$$AE_{s-ITD} < AE_{s-CPR} + 5\%$$

Farrington and Manning method was specified for the secondary safety endpoint analysis.

Secondary Effectiveness Endpoint Hypothesis (superiority)

s-CPR vs. ACD-ITD

H₀: The mean CASI Score for patients receiving ACD-ITD is equal to or less than that for patients receiving s-CPR.

$$CASI_{ACD-ITD} \leq CASI_{s-CPR}$$

H₁: The mean CASI Score for patients receiving ACD-ITD is greater than that for patients receiving s-CPR.

$$CASI_{ACD-ITD} > CASI_{s-CPR}$$

s-CPR vs. s-ITD (*this analysis was subsequently abandoned due to dropping of the s-ITD arm from the study*)

H₀: The mean CASI Score for patients receiving s-ITD is equal to or less than that for patients receiving s-CPR.

$$CASI_{s-ITD} \leq CASI_{s-CPR}$$

H₁: The mean CASI Score for patients receiving s-ITD is greater than that for patients receiving s-CPR.

$$CASI_{s-ITD} > CASI_{s-CPR}$$

A t-test was specified for the secondary effectiveness endpoint analysis.

Appendix 2

Sample Size

The *primary endpoint*:

In the original protocol (dated 9/12/05), under the original interim analysis plan, the sponsor claimed that 700 evaluable subjects in each of the three treatment arms would have 80% power to detect a clinical difference of 4.9% if the s-CPR survival rate was 6%. The test method was the Chi-square method in the sample size calculation. For the primary endpoint analysis, however, the test method was the Fisher's exact test. It was anticipated that up to 3100 patients would need to be enrolled to obtain 2100 evaluable patients who satisfied the final inclusion criteria.

The *secondary safety endpoint*:

In the original protocol, under the original interim analysis plan, the sponsor claimed that 411 evaluable subjects in each of the three treatment groups would have 80% power to conclude non-inferiority with the non-inferiority margin of 5% if the s-CPR major adverse event rate was 94%. The test method was the Farrington and Manning method.

In the new protocol, with the revised interim analysis plan, the sample size was decreased to 304 evaluable subjects in the s-CPR and ACD-ITD arms. The event rate assumption and the test method remained the same.

The *secondary effectiveness endpoints*:

The effect size (difference/standard deviation) was assumed to be one. A total of 21 subjects in each treatment group would have a power of 80% at a two-sided alpha level of 0.05 with a t-test.

Appendix 3

Drug overdose

There were 179 overdose subjects, including: 2 s-CPR subjects, 4 ACD-ITD subjects, and 1 s-ITD subject at **run-in** phase; 65 s-CPR subjects, 98 ACD-ITD subjects, and 9 s-ITD subjects at **pivotal** stage.

Table17. Proportion of Subjects with Drug Overdose in ITT population (by the FDA)

| S-CPR | ACD-ITD |
|-----------------|-----------------|
| 5.41% (65/1201) | 7.72% (98/1269) |

Table18. Primary Endpoint for the Overdose Subjects, mITT, complete case analysis (by the FDA)

| S-CPR (N=65) | ACD-ITD (N=98) |
|----------------|-------------------------|
| 15.38% (10/65) | 9.28% (9/97), 1 missing |

It is noteworthy that significantly higher proportion of ACD-ITD subjects than the s-CPR subjects in the ITT population were identified as drug overdose and all the overdose subjects (65 s-CPR and 98 ACD-ITD) were excluded from the mITT analysis population. To investigate the impact of these excluded overdose subjects on the analysis results, we added these 163 subjects in the mITT and as-treated analyses.

Superiority cannot be met if the overdose subjects included in either the mITT or the as-treated analysis.

Table 19. Primary Endpoint Rate, mITT/as-treated plus drug overdose subjects (Complete Case) (by the FDA)

| Analysis Population | Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------|------------------------------------|--------------------|--------------------|------------------------|
| mITT | All S-CPR vs. ACD-ITD [#] | 6.59% (57/865) | 8.98% (84/935) | 0.0652 |
| | First 1400 subjects | 6.82% (47/689) | 9.46% (66/698) | 0.0776 |
| | CHW | 6.59% (57/865)* | 8.98% (84/935)* | 0.0882** |
| As-Treated Method 1 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.30% (75/904) | 0.2057 |
| | First 1400 subjects | 6.91% (47/680) | 8.88% (60/676) | 0.1912 |
| | CHW | 6.67% (57/855)* | 8.30% (75/904)* | 0.2624** |
| As-Treated Method 2 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.20% (71/866) | 0.2336 |
| | First 1400 subjects | 6.91% (47/680) | 8.63% (56/649) | 0.2598 |
| | CHW | 6.67% (57/855)* | 8.20% (71/866)* | 0.3172** |
| As-Treated Method 3 | All S-CPR vs. ACD-ITD [#] | 7.45% (66/886) | 8.15% (71/871) | 0.5946 |
| | First 1400 subjects | 7.55% (53/702) | 8.58% (56/653) | 0.5489 |
| | CHW | 7.45% (66/886)* | 8.15% (71/871)* | 0.7212** |
| As-Treated Method 4 | All S-CPR vs. ACD-ITD [#] | 6.67% (57/855) | 8.98% (84/935) | 0.0788 |
| | First 1400 subjects | 6.91% (47/680) | 9.46% (66/698) | 0.0951 |
| | CHW | 6.67% (57/855)* | 8.98% (84/935)* | 0.1024** |

[#]: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Delayed CEC Adjudication of 28 mITT patients

Table 20. Primary Endpoint Rate, mITT plus 28 delayed adjudicated subjects (Complete Case) (by the FDA)

| Analysis Population | Approach | S-CPR | ACD-ITD | 2-sided p-value |
|----------------------------|---------------------|--------------------|--------------------|------------------------|
| mITT | S-CPR vs. ACD-ITD# | 6.20% (50/806) | 8.84% (76/860) | 0.0512 |
| | First 1400 subjects | 6.48% (44/679) | 9.17% (65/709) | 0.0722 |
| | CHW | 6.20% (50/806)* | 8.84% (76/860)* | 0.0642** |
| As-Treated Method 1 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.17% (68/832) | 0.1520 |
| | First 1400 subjects | 6.57% (44/670) | 8.59% (59/687) | 0.1826 |
| | CHW | 6.28% (50/796)* | 8.17% (68/832)* | 0.1966** |
| As-Treated Method 2 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.03% (64/797) | 0.2062 |
| | First 1400 subjects | 6.57% (44/670) | 8.35% (55/659) | 0.2504 |
| | CHW | 6.28% (50/796)* | 8.03% (64/797)* | 0.2534** |
| As-Treated Method 3 | S-CPR vs. ACD-ITD# | 7.04% (58/824) | 7.98% (64/802) | 0.5102 |
| | First 1400 subjects | 7.23% (50/692) | 8.30% (55/663) | 0.4782 |
| | CHW | 7.04% (58/824)* | 7.98% (64/802)* | 0.6042** |
| As-Treated Method 4 | S-CPR vs. ACD-ITD# | 6.28% (50/796) | 8.84% (76/860) | 0.0518 |
| | First 1400 subjects | 6.57% (44/670) | 9.17% (65/709) | 0.0892 |
| | CHW | 6.28% (50/796)* | 8.84% (76/860)* | 0.0752** |

#: This analysis was performed without taking the interim looks into consideration. As such, drawing conclusions from the p-values are difficult because of the study issues identified above.

*: This rate is just the overall event rate by directly pooling stage 1 (before the interim look) and stage 2 (after the interim look).

** : two-sided p-value could not be directly calculated, so this p-value was calculated by 2 x one-sided p-value

Appendix 4

Please note that the mITT analysis population just indicates which subjects should be included in the analysis. However, it does not indicate how to handle the missing data. Usually we handle missing data through three different methods **within** an analysis population: 1) complete-case analysis; 2) Multiple imputation; 3) Sensitivity analysis (to be more specific for this study, tipping point analysis). To illustrate these three methods, we have the following table.

| Method | Underlying Missing Data Mechanism | Method Description | Concerns |
|---|--|--|--|
| Complete-case Analysis | Missing Completely At Random (MCAR): missingness does not depend on the observed or unobserved measurements | Under the MCAR assumption bias won't be introduced by ignoring the missing data. Therefore this method only analyzes the observed data and ignores the missing data by deleting the subjects with missing data from the analysis. | We need to check the robustness of the study conclusion based on this analysis, i.e., we need to check whether the study conclusion remains the same when the MCAR assumption is invalid. |
| Multiple Imputation | Missing At Random (MAR): missingness depends only on the observed values, not on the unobserved measurements. | Under the MAR assumption, the behavior of the post dropout observations can be predicted from the observed variables. Therefore this model using the available data to set up a statistical model to impute the missing data, and then uses the imputed dataset to perform the analysis. | This method relies on the MAR assumption, which is not testable from the observed data. In addition, the model-based estimates may be very sensitive to misspecification of the model. Therefore, sensitivity analyses are needed. |
| Sensitivity Analysis: Tipping point analysis | No need to postulate the missing data mechanism | This method examines every scenario which may occur in the missing data group (for the binary outcomes). | It helps to see how much the study conclusion changes for various missing data mechanisms. Consistent sensitivity analysis results provide assurance of the robustness of the study conclusion. |

Appendix 5

Table 21. Patients with missing mRS values

| Subject ID | GROUP | SITE | INCIDENT_Sect1 | AGE |
|------------|-------------|-------|----------------|-----|
| (b)(6) | S-CPR | 10001 | 9/5/2006 | 48 |
| | S-CPR | 10001 | 12/11/2007 | 83 |
| | S-CPR | 10002 | 3/8/2007 | 74 |
| | S-CPR | 10002 | 3/13/2007 | 62 |
| | S-CPR | 10003 | 7/25/2009 | 70 |
| | S-CPR | 10005 | 3/4/2007 | 44 |
| | S-CPR | 10005 | 5/18/2007 | 69 |
| | S-CPR | 10005 | 7/24/2007 | 46 |
| | S-CPR | 10006 | 12/19/2007 | 60 |
| | S-CPR | 10006 | 8/13/2008 | 52 |
| | S-CPR | 10007 | 4/21/2009 | 44 |
| | S-CPR | 10007 | 6/20/2009 | 87 |
| | S-CPR | 10007 | 7/26/2009 | 58 |
| | ACD-CPR+ITD | 10002 | 10/12/2006 | 50 |
| | ACD-CPR+ITD | 10002 | 3/2/2007 | 47 |
| | ACD-CPR+ITD | 10005 | 2/12/2008 | 97 |
| | ACD-CPR+ITD | 10007 | 4/19/2009 | 63 |