California Cardiac Solutions: Four Chamber Redundant Impeller Artificial Heart Device Regulatory and Reimbursement Strategy

Prepared for: Peter DeSilva, MD
California Cardiac Solutions
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III. Project Overview Timeline
I. NAMSA Regulatory Strategy

Device Name: Four Chamber Redundant Impeller Artificial Heart Device

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Current devices on the U.S. market intended for use as an artificial heart or for cardiac assist were researched by NAMSA. There is really only one Total Heart on the market, which is the Syncardia Temporary CardioWest Total Artificial Heart (TAH-T). A sampling of Ventricular Assist System Devices and currently marketed temporary device technologies is presented in Table 2 of this report.

The review of currently marketed technologies did not identify a device similar to the Four Chamber Redundant Impeller Artificial Heart Device. The devices reviewed are currently approved for short-term use during interventional procedures, during acute recovery of myocardial function, as a bridge to transplant (BTT), or as a destination therapy (DT).

The Abiocor replacement heart (AbioMed) was a totally implantable artificial heart intended as a permanent cardiac replacement. According to UnitedHealthcare, the AbioCor is no longer being manufactured, but has been included as an example in the reimbursement space of this report to demonstrate how a permanent cardiac replacement device has been covered by private insurers in the past.
1. Executive Summary

1.1 Overview

This regulatory strategy prepared by NAMSA outlines the U.S. regulatory requirements and submission pathway for the novel Four Chamber Redundant Impeller Artificial Heart device. A review of relevant U.S. medical device regulations and clinical studies was performed to identify pre-clinical and clinical testing required to support approval of the device.

The Four Chamber Redundant Impeller Artificial Heart technology is unique as compared to currently marketed heart assist devices. It will be considered a Class III, high-risk device by FDA and will require an Investigational Device Exemption (IDE) and Premarket Approval Application (PMA) approval prior to placement on the U.S. market.

Extensive pre-clinical testing will be required prior to conducting the IDE human clinical study. Pre-clinical testing will include design verification testing, biological safety testing, software validation, electrical safety testing, usability and animal testing.

Human clinical testing protocols will require review and approval by FDA and Institutional Review Boards prior to starting clinical trials. The clinical testing should be conducted in phases beginning with a small feasibility safety study and then expanded into a larger pivotal study. After completion of successful clinical studies, a PMA submission will be required containing safety, efficacy and manufacturing information.

FDA will base their PMA approval decision on the following criteria:

- reasonably assurance that a device is safe and effective
- valid scientific evidence that the probable benefits to health from the intended use of a device outweigh the probable risks
- the device will significantly help a large portion of the target population

Additionally, as part of the PMA approval process, the device manufacturing facility must be compliant with the FDA Quality Management System regulation. It is recommended to implement design controls early in the development process and to have well developed quality systems in place prior to the IDE clinical study.

1.2 Assumptions

The information in this report is, to the best of our knowledge, an accurate representation of the current regulatory requirements in the United States. The medical device laws, regulations and guidance are subject to change by the FDA and actual practices may differ from the published laws, regulations and guidance documentation.
2. Background and Product Description
The company, California Cardiac Solutions (CCS), is developing a novel and miniaturized Total Artificial Heart for treatment of late stage congestive heart failure (CHF). The Four Chamber Redundant Impeller Artificial Heart will incorporate miniaturized, novel technology that is completely implanted. The combination of fluid dynamics, smoothed pump mechanics, biocompatible blood surfaces, and non-invasive energization will be designed to provide functionality and durability not seen in other designs. The CCS technology has been protected with a combination of patent (US Patent 9,314,559) and trade secret data.

The Four Chamber Redundant Impeller Artificial Heart for human recipients consists of a housing containing four segmented, operative turbine pumps. The four-turbine pump design provides a redundancy to enhance safety of the artificial heart. A dual controller will monitor pressure transducer sensor data and will control the performance and function of the artificial heart. The battery will be implanted, along with the controller, to eliminate the need for external connections. An inductively coupled battery charger will provide inductively coupled charging for use in driving the artificial heart.

To implant the device, the first of the blood inputs will be coupled to the source of returning blood supply from the patient’s vena cava. The output of the corresponding pump section will be coupled to the pulmonary artery. The remaining pump input will be coupled to the pulmonary vein carrying the blood returning from the recipient’s lungs and the corresponding pump output stage will be coupled out to the recipient’s body via the recipient’s aorta.

3. Proposed Indication for Use
It is expected that the Four Chamber Redundant Impeller Artificial Heart will pursue both Bridge to Transplant (BTT) and permanent implant Destination Therapy (DT) indications for use. A proposed strategy would be to initially pursue a BTT indication for use and to expand the indication for DT as more long term safety data is collected.

Current approved heart assist devices are indicated for short term temporary use, for use as a bridge to transplant (BTT) or for longer term destination therapy (DT).

4. Device Classification
The U.S. FDA classifies medical devices as Class I, II, or III according to risk the device poses to the patient and/or end-user. Class I includes devices with the lowest risk and Class III includes those with the greatest risk. The class to which a device is assigned determines, among other things, the type of premarketing submission or application required for FDA clearance or approval.

The following submission or application requirements are generally true:
- Class I (General Controls) – no submission prior to marketing
- Class II (Special Controls) – Premarket Notification [510(k) submission]
- Class III - Premarket Approval (PMA)
The Four Chamber Redundant Impeller Artificial Heart device, a high-risk, life-sustaining device, will be considered a Class III device using FDA’s classification criteria.

FDA further classifies devices by use of product codes (a three letter code that categorizes devices based on primary device features and intended use). A review of FDA product codes associated with heart assist devices was conducted. A summary of the current codes is given in Table 1.

### Table 1 – FDA Product Codes for Heart Assist Devices

<table>
<thead>
<tr>
<th>FDA Product Code</th>
<th>Device Name</th>
<th>Definition</th>
<th>Device Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>OZD</td>
<td>Temporary Non-Roller Type Cardiac Support Blood Pump</td>
<td>Blood pump that provides temporary full or partial cardiac/ventricular support as an adjunctive therapy for patients considered high risk for cardiac procedures</td>
<td>PMA – Class III</td>
</tr>
<tr>
<td>LOZ</td>
<td>Artificial Heart</td>
<td>Assigned to Syncardia Temporary Total Artificial Heart PMA 0300011</td>
<td>PMA – Class III</td>
</tr>
<tr>
<td>OKR</td>
<td>Ventricular Bypass (Assist) Device</td>
<td>A ventricular bypass (assist) device is a device that assists the left or right ventricle in maintaining circulatory blood flow for &lt;6 hours. The device is either totally or partially implanted in the body.</td>
<td>PMA – Class III</td>
</tr>
<tr>
<td>DSQ</td>
<td>Ventricular (Assist) Bypass Device</td>
<td>Assigned to Thoratec PMA P870072</td>
<td>PMA – Class III</td>
</tr>
</tbody>
</table>

Although some features defined in existing product codes align with features of the Four Chamber Redundant Impeller Artificial Heart, it is likely FDA would assign a new product code for the novel totally implantable artificial heart technology.

Independent of the specific product code assigned, the Four Chamber Redundant Impeller Artificial Heart device will be regulated by FDA as a Class III, high-risk, PMA device reviewed by FDA’s Circulatory Support Devices Branch.

5. Competitive Devices Currently on the U.S. Market

Current devices on the U.S. market intended for use as an artificial heart or for cardiac assist were researched by NAMSA. A sampling of the TAH-T along with Ventricular Assist System Devices and currently marketed temporary device technologies is presented in Table 2.

### Table 2 – Current U.S. Approved Implantable Artificial Heart or Cardiac Support Blood Pumps
<table>
<thead>
<tr>
<th>Device Name/Sponsor</th>
<th>PMA/Original Decision Date/FDA Product Code</th>
<th>Indications for Use</th>
<th>Description of the System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoratec HeartMate® II Left Ventricular Assist System (LV AS)</td>
<td>P060040 April 21, 2008</td>
<td>The HeartMate II LV AS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate II L VAS is intended for use both inside and outside the hospital, or for transportation of ventricular assist device patients via ground ambulance, fixed-wing aircraft, or helicopter.</td>
<td>The HeartMate II Left Ventricular Assist System (LV AS) consists of an implanted axial flow blood pump and external components. Electrical power to the implanted blood pump is delivered through a percutaneous lead that connects to an external System Controller. The System Controller is powered by a Power Base Unit (PBU) that connects to AC mains power, or by two batteries that the patient carries or wears in shoulder holsters.</td>
</tr>
<tr>
<td>Thoratec Corporation</td>
<td>PMA 060040 S005 January 2010</td>
<td>The HeartMate II is approved for use in patients with New York Heart Association (NYHA) Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and who are not candidates for cardiac transplantation.</td>
<td></td>
</tr>
<tr>
<td>HeartWare® Ventricular Assist System</td>
<td>P100047 November 20, 2012</td>
<td>The HeartWare Ventricular Assist System (HeartWare VAS) is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The Heart Ware VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter.</td>
<td>Implanted components of the HeartWare VAS include the pump (which includes an integrated inflow cannula), an outflow conduit, a percutaneous driveline, and an apical sewing ring. The Heart Ware ventricular assist device (HVAD) pump is a continuous flow blood pump which utilizes magnetic and hydrodynamic forces to elevate and rotate the impeller. Once power is applied to the device, there are no points of mechanical contact between the impeller and the body of the pump. The pump displaces 50mL of blood, weighs 160g, and is capable of pumping up to 10 liters per minute (L/min) of blood. External components include the controller,</td>
</tr>
<tr>
<td>Device Name/Sponsor</td>
<td>PMA/Original Decision Date/FDA Product Code</td>
<td>Indications for Use</td>
<td>Description of the System</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------</td>
<td>---------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Syncardia Temporary CardioWest Total Artificial Heart (TAH-T)</td>
<td>P030011 October 15, 2004 FDA Product Code LOZ – Artificial Heart</td>
<td>The SynCardia Systems, Inc., CardioWest temporary Total Artificial Heart (hereinafter called the TAH-t) is indicated for use as a bridge to transplantation in cardiac transplant eligible candidates at risk of imminent death from biventricular failure. The CardioWest TAH-t System is intended for use inside the hospital. Note: Clinical study underway for Destination Therapy indication for use.</td>
<td>The SynCardia Cardio West TAH-t system is a pulsatile biventricular device that is placed after the native ventricles are excised. The implantable device consists of two artificial ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. These diaphragms allow the ventricles to fill and then eject blood when compressed by air from the external drive console. Mechanical valves mounted in the inflow (27 mm) and outflow (25 mm) ports of each artificial ventricle control the direction of blood flow. The maximum dynamic stroke volume of each artificial ventricle is 70 ml, which allows for generating a flow rate up to 9.5 l/min. Each artificial ventricle's driveline conduit is tunneled through the chest. The driveline conduit is covered with velour fabric on its external surface to promote tissue growth. The right and left driveline conduits are attached to seven-foot drivelines that connect to the back of the external drive console.</td>
</tr>
<tr>
<td>Device Name/Sponsor</td>
<td>PMA/Original Decision Date/FDA Product Code</td>
<td>Indications for Use</td>
<td>Description of the System</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Impella System</td>
<td>P140003</td>
<td>Indication #1</td>
<td>The Impella 2.5 System is comprised of three components manufactured by ABIOMED:</td>
</tr>
<tr>
<td></td>
<td>March 23, 2015</td>
<td>The Impella 2.5 and the Impella CP are temporary (&lt;6 hours) ventricular support systems indicated for use during high-risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA Product Code OZD</td>
<td>Indication #2</td>
<td>The Impella 2.5 System is a minimally invasive, miniaturized percutaneous circulatory support system that is placed across the aortic valve via a single femoral arterial access. The Impella 2.5 Catheter consists of a micro-axial rotary blood pump mounted on a 9F catheter. The Impella 2.5 Catheter can be percutaneously inserted through the femoral artery and positioned across the aortic valve into the left ventricle. The device actively unloads the left ventricle by pumping blood from the ventricle into the ascending aorta and systemic circulation. When in place, the Impella 2.5 Catheter can be driven by the AIC to provide up to 2.5 liters/minute of partial left ventricular support.</td>
</tr>
<tr>
<td></td>
<td>Temporary Non-Roller Type Cardiac Support Blood Pump</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The review of currently marketed technologies did not identify a device similar to the Four Chamber Redundant Impeller Artificial Heart. The devices reviewed are currently approved for
short-term use during interventional procedures, during acute recovery of myocardial function, as a bridge to transplant (BTT) or as destination therapy (DT).

6. Development Pathway for U.S Market Approval

6.1 Regulatory Overview
The Four Chamber Redundant Impeller Artificial Heart must demonstrate safety and efficacy for its intended use prior to market approval in the U.S. The pathway for U.S. approval of this high-risk device will be to conduct a clinical study via an Investigational Device Exemption (IDE) followed by a Premarket Approval Application (PMA).

FDA has also created an alternative pathway for devices that will treat rare conditions afflicting less than 4000 persons a year in the U.S., the Humanitarian Device Exemption. Although this pathway could be explored for a unique sub-set of patients, it is unlikely this pathway would be viable for the artificial heart due to the availability of existing treatments for people suffering from advanced HF.

6.2 Pre-Clinical Testing
Prior to use in humans, the four chamber artificial heart must undergo extensive pre-clinical testing including biological safety testing, design verification testing and feasibility testing in an animal model. An overview of the types of testing required for the artificial heart is summarized below.

Note: The pre-clinical testing intended to support safety of the final device should be reviewed by FDA to ensure the testing will meet FDA’s requirements.

6.3 Biocompatibility Testing
Biocompatibility testing will be required to support biological safety and physiologic compatibility of the artificial heart. ISO 10993-1:2009 Biological evaluation of medical devices Part 1: Evaluation and testing in the risk management process provides the basis for planning and conducting biological safety testing for medical devices.

The ISO 10993 standard provides device testing guidance based on the intended use, tissue contacting designation and duration of body contact with the device. The artificial heart implant will be classified as a permanent implant device (>30 days) with circulating blood contact.

The testing conducted to support an IDE should be performed on final, packaged, sterile devices. Proposed biocompatibility testing should be reviewed with FDA as part of the pre-submission process. NAMSA can also provide support when planning and presenting the biological safety testing proposal.

The biocompatibility testing typically required for implanted heart devices is listed in Table 3 below.
Table 3 – Typical Biocompatibility Testing Required for Permanent Implant Device with Blood Contact

<table>
<thead>
<tr>
<th>Testing</th>
<th>Method Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity</td>
<td>ISO 10993-5: Biological Evaluation of Medical Devices-Tests for In Vitro Cytotoxicity</td>
</tr>
<tr>
<td>Sensitization</td>
<td>ISO 10993-10: Biological Evaluation of Medical Devices- Tests for Irritation and Delayed-Type Hypersensitivity</td>
</tr>
<tr>
<td>Irritation- Intracutaneous Injection</td>
<td>ISO 10993-10: Biological Evaluation of Medical Devices- Tests for Irritation and Delayed-Type Hypersensitivity.</td>
</tr>
<tr>
<td>Acute Systemic Toxicity</td>
<td>ISO 10993-11: Evaluation of Medical Devices- Tests for Systemic Toxicity</td>
</tr>
<tr>
<td>Material Mediated Rabbit Pyrogen</td>
<td>ISO 10993-11: Evaluation of Medical Devices- Tests for Systemic Toxicity</td>
</tr>
<tr>
<td>Subacute and Subchronic Toxicity</td>
<td>ISO 10993-11: Evaluation of Medical Devices- Tests for Systemic Toxicity</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>ISO 10993-3: Evaluation of Medical Devices- Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity</td>
</tr>
<tr>
<td>Implantation</td>
<td>ISO 10993-6:2007 Evaluation of Medical Devices- Tests for local effects after implantation</td>
</tr>
<tr>
<td>Hemocompatibility</td>
<td>ISO 10993-4: Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood</td>
</tr>
<tr>
<td>Extraction Study and Chemical Analysis</td>
<td>ISO 10993-17:2002 Establishment of allowable limits for leachable substances</td>
</tr>
<tr>
<td>Toxicological Risk Assessment</td>
<td>ISO 10993-18:2005 Chemical characterization of Materials</td>
</tr>
</tbody>
</table>

6.4 Design Verification Testing
Design verification testing (DVT) will be required to ensure the artificial heart device and its packaging meet reliability, performance and functional requirements. Functional and performance testing for the artificial heart would include the types of testing discussed below.

In-vitro Flow Characterization
In vitro characterization should be conducted on a simulated circulatory loop to test the device over various pressures and flow rates.

Reliability Testing
Reliability testing is conducted to determine the expected life-time performance and fatigue resistance of the device. The testing can be conducted with bench top modeling and should be performed on newly manufactured devices and on devices aged up to the designated shelf-life designation.
Functional/Mechanical Testing
Structural and integrity testing for the artificial heart and its packaging would include the types of testing listed below. This list is not all-inclusive and there may be unique testing requirements specific to the design of the artificial heart.

- Material Integrity Testing
- Tensile Testing – Joint/Connector Testing
- Flow Accuracy
- Pressure Accuracy
- Simulated Placement
- Fluid Dynamic Testing
- Hemolysis Testing
- Sensor Testing
- Battery Testing - Longevity
- Full System Performance
- Packaging Integrity Testing

Sterilization Validation
All sterile components of the device system must undergo sterilization validation testing. The validation must be conducted on final, packaged devices before product can be released for human use. Ethylene oxide is a widely used sterilization method for implantable heart devices. A sterilization validation can be expected to take from 3 to 6 months.

Shelf Life Testing
A designated shelf life for the device and its packaging must be supported with packaging integrity and device performance testing after simulated accelerated and real time aging. It is best practice to design and test packaging along with the device.

Software
Verification and validation testing of the device software will be required prior to human use of the device. FDA classifies device software as having a low, moderate or high level of concern based on intended use. Software controlling the artificial heart will be designated as a “high level of concern.”

Software development and testing should be conducted according to FDA’s software guidance document, General Principles of Software Validation; Final Guidance for Industry and FDA Staff – January 11, 2002. Extensive software development documentation will be required as part of the IDE and PMA device submissions reviewed by FDA.

Electrical Safety/EMC
Electrical safety testing will be required for the artificial heart and its electrical components prior to human use. The testing should include electromagnetic compatibility testing (EMC),
electromagnetic immunity testing (EMI) and electrical safety testing conducted according to recognized standards.

The general standard used for medical device electrical testing is *IEC 60601-1 Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*. Collateral standards within the IEC 60601 standard series should also be assessed for applicability prior to developing a comprehensive electrical testing plan. It is best practice to have a collaborative review with an electrical testing expert to ensure electrical safety risks have been appropriately addressed.

**Usability- Human Factors Testing**
Usability testing will be required to assess the user/device interface and to identify safety issues associated with potential use error. FDA guidance document *Applying Human Factors and Usability Engineering to Medical Devices February 3, 2016* provides an overview of FDA’s expectations for usability engineering studies. NAMSA can provide support in design of human factors studies.

**6.5 Animal Testing**
Testing of the artificial heart in an animal model will be required to demonstrate feasibility and safety prior to human use. Animal studies are intended to test potential thrombogenic and hemolytic characteristics of the device system and to demonstrate effective in vivo device performance.

Studies for heart implant devices are typically performed in a bovine or ovine model. Acute studies (up to 90 days) can be conducted in a calf model before the animal outgrows the device while longer term studies are typically conducted in the ovine model.

For reference, animal testing supporting approval of the HeartMate was conducted on 65 calves during the device development. Five calves were implanted with the final clinical device and were studied for up to 30 days (3 calves) or 90 days (2 calves) post-implant. For comparison, nine sheep were studied for a period of 90 days to support approval of the Heartware LVAD device.

FDA may require longer-term survival studies in an animal model (6 months to 1 year) prior to a human clinical study for destination therapy. Due to the large expense and time commitment involved with animal studies it is important to discuss the animal testing protocol with FDA as part of pre-IDE meeting discussions.
7. Human Clinical Studies

7.1 Overview of Device Studies
Clinical studies for novel devices are typically conducted in stages, starting with a small-scale pilot study to assess safety, followed by a larger, multi-site pivotal study conducted with a representative treatment population. Human clinical studies can be initiated after FDA and an Institutional Review Board have reviewed an Investigational Device Exemption (IDE) and has allowed the study to proceed.

NAMSA performed a review of recently conducted and on-going clinical studies for heart assist devices to provide an overview of study designs that may be appropriate to support FDA approval of the Four Chamber Redundant Impeller Artificial Heart. A sampling of devices and their clinical study designs is given in Table 4.

<table>
<thead>
<tr>
<th>Device</th>
<th>Approved or Investigational Device</th>
<th>Approved or Proposed Indication</th>
<th>Summary of Study Design/Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartMate II LVAD</td>
<td>Approved Device</td>
<td>BTT</td>
<td>Multi-Center, Non-Randomized Prospective Study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pivotal Study – 133 Subjects /26 Sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continued Access – 146 Subjects / 26 Sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Year Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary Endpoint: Survival to cardiac transplantation or 180 days on LVAS support while maintaining listed for cardiac transplant as UNOS status 1A or 1B.</td>
</tr>
<tr>
<td>HeartMate II LVAD</td>
<td>Approved Device</td>
<td>DT</td>
<td>Multi-Center, Randomized Prospective Study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pivotal Study – 200 Subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Year Follow-Up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary Endpoint: Survival at two years, free of stroke, or reoperation to repair the device.</td>
</tr>
<tr>
<td>Device</td>
<td>Approved or Investigational Device</td>
<td>Approved or Proposed Indication</td>
<td>Summary of Study Design/Endpoints</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------</td>
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<td>---------------------------------</td>
</tr>
</tbody>
</table>
| Syncardia Temporary CardioWest Total Artificial Heart (TAH-T) 70cc | Approved Device | BTT | Study Design: Non-Randomized, Multi-Center (5 sites) with both Historical and Concurrent Controls 2 Year Follow-Up  
Pivotal Study: 95 Subjects (81 Subject Core Implant Group)  
Effectiveness Parameter(s): Patients who, at 30 days post-transplant were alive, NYHA Class I or II, not bedridden, not ventilator dependent and not requiring dialysis  
Survival to Transplant |
| Syncardia 50cc TAH-t | Investigational NCT02459054 | BTT | Study Design:  
- Three Arm Non-Randomized Study  
  Primary Pediatric Arm  
  Primary Adult Arm  
  Secondary Arm (Pediatric and Adult)  
Estimated Enrollment: 72 Subjects  
Effectiveness Parameter(s): Probable benefit to transplant eligible patients |
| Syncardia 70cc TAH-t | Investigational NCT02232659 | DT | Study Design: To determine if the device can support patients with HF who are not eligible for transplant.  
Estimated Enrollment: 38 Subjects  
Effectiveness Parameter(s): Survival to 6 months without experiencing permanent disabling stroke-related deficits. Follow-up to be conducted for 5 years. |
<p>| Impella 2.5 System | Approved Device | Temporary Support | Feasibility Study: PROTECT I |</p>
<table>
<thead>
<tr>
<th>Device</th>
<th>Approved or Investigational Device</th>
<th>Approved or Proposed Indication</th>
<th>Summary of Study Design/Endpoints</th>
</tr>
</thead>
</table>
|                                    |                                    | (≤6 Hours ventricular support during PCI) | Prospective, multi-center, single arm study (7 sites)  
20 Subjects Enrolled  
Pivotal Study: PROTECT II  
Prospective, multi-center, randomized control study (112 sites)  
452 Subjects Enrolled  
USSpella Registry:  
Retrospective, multi-center voluntary registry (49 sites)  
637 Patients in High Risk PCI Cohort  
Effectiveness Parameters: Demonstrate the Impella 2.5 System was superior to IABP in preventing intra and post procedural Major Adverse Events (MAE) |
| HeartWare® Ventricular Assist System| Approved Device                    | BTT                             | Study Design: Non-randomized, contemporaneous controlled trial.  
Pivotal Study: 140 Subjects in Test Arm and 499 Subjects in Control Arm  
Primary Endpoint: Success at 180 days defined as alive on the originally implanted HeartWare or transplanted or explanted for recovery. |
| HeartAssist5                        | Investigational NCT02205411         | BTT                             | Study Design: Prospective, randomized, multi-center trial comparing the HeartAssist 5® to the Thoratec HeartMate II and Heartware HVAD in patients awaiting cardiac transplantation.  
Estimated Enrollment: 192 Subjects  
Primary Endpoint: Success at 180 days defined as alive on the original device, |
### 7.2 Clinical Study Review Conclusions

The following conclusions are based on NAMSA’s review of recently conducted or on-going studies for heart assist devices. As FDA’s expectations may change over time and when reviewing new technologies, these conclusions are intended for preliminary planning purposes only.

#### Number of Subjects

A review of recently conducted or on-going studies showed that feasibility studies were conducted with about 20 subjects. Enrolled pivotal study subjects were in the range of about 100 to 200 subjects with post-approval registries enrolling upwards of 600+ patients.

It is expected that FDA would require enrollment of approximately 20 subjects in a pilot study supporting safety of the four chamber artificial device. The pivotal trial would be estimated to require enrollment of about 200 subjects.

#### Primary Study Endpoint

The primary efficacy endpoint for Bridge to Transplant would likely be survival to transplant or survival up to 180 days while on the transplant list. For Destination Therapy, FDA may require survival endpoints extended up to 2 years.

<table>
<thead>
<tr>
<th>Device</th>
<th>Approved or Investigational Device</th>
<th>Approved or Proposed Indication</th>
<th>Summary of Study Design/Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Pulse Sunshine Heart</td>
<td>NCT00815880 Investigational</td>
<td>Reduction of Symptoms of HF</td>
<td>Feasibility Study: Phase 1, single arm study with 20 subjects. Safety Endpoint: Composite review of device related adverse events through 6 months.</td>
</tr>
<tr>
<td>C-Pulse Sunshine Heart</td>
<td>NCT01740596 Investigational</td>
<td>Reduction of Symptoms of HF</td>
<td>Pivotal Study: Prospective, multi-center, randomized trial as compared to optimal medical therapy. Estimated Enrollment: 38 Subjects Primary Endpoint: 1 Year Follow-Up measuring freedom from worsening HF requiring hospitalization, LVAD implantation, cardiac transplant or death.</td>
</tr>
</tbody>
</table>

transplanted or explanted for heart recovery and alive 60 days after device explant.
**Post-Market Study**
A post-market registry study will likely be required by FDA as part of the PMA approval process. FDA typically requires large numbers of patients in post-marketing registries to understand adverse events occurring during widespread use of the device.

It should be noted that there are a number of on-going studies for heart assist devices as documented in the clinicaltrial.gov website. For this reason, competition for subject enrollment should be considered when estimating subject enrollment rates.

**FDA Pre-IDE Meeting**
A FDA pre-IDE meeting to review the proposed human clinical study design will be a critical step in the regulatory pathway. The number of subjects, number of sites, inclusion/exclusion criteria, informed consents, statistical study plans, control arms and study endpoints must all be thoroughly discussed and agreed upon.

**8. Applicable Development Documents**
The following section lists FDA guidance documents and international standards that may be applicable to the design and development of the four chamber artificial heart. This list should not be considered all-inclusive but is intended to reference primary standards that should be considered. FDA maintains a list of recognized standards and encourages their use but does not mandate use of standards.

8.1 FDA Guidance Documents
- General Principles of Software Validation; Final Guidance for Industry and FDA Staff – January 11, 2002
- Applying Human Factors and Usability Engineering to Medical Devices; Guidance for Industry and FDA Staff – February 3, 2016

8.2 International Standards
- ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.
- ISO 14971, Medical devices – Application of risk management to medical devices
- IEC 60601-1 Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
- ISO 14708-5 First edition 2010-02-01 - Implants for surgery - Active implantable medical devices - Part 5: Circulatory support devices
- ISO 14155, Clinical investigation of medical devices for human subjects — Good clinical practice
- IEC 62304:2006, Medical device software — Software life cycle processes
9. Regulatory Submissions and FDA Interactions

The U.S. regulatory pathway for the four chamber artificial heart would require an Investigational Device Exemption (IDE) clinical study followed by a Premarket Approval Application (PMA) to FDA. The major regulatory activities required or recommended are summarized in Table 5.

<table>
<thead>
<tr>
<th>Regulatory Activity</th>
<th>Estimated Time</th>
<th>FDA Fees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Clinical Study Meeting and Pre-IDE Submission Meeting with FDA (Recommended)</td>
<td>70-90 Days from Meeting Request Date</td>
<td>None</td>
</tr>
<tr>
<td>IDE Submission</td>
<td>30 Day Initial Review Time (Approval to proceed may take 3-6 months)</td>
<td>None</td>
</tr>
<tr>
<td>Pre-PMA Submission Meeting with FDA (Recommended)</td>
<td>70-90 Days from Meeting Request Date</td>
<td>None</td>
</tr>
<tr>
<td>Post-Approval Studies</td>
<td>Variable – Determined by FDA</td>
<td>None</td>
</tr>
</tbody>
</table>

9.1 FDA Pre-Submission Meetings

The regulatory strategy should begin very early in the development cycle of a medical device. Due to the large investment of money, time and resources, it is important to receive buy-in from FDA prior to planning pre-clinical and clinical studies.

FDA encourages use of the pre-submission meeting program to provide early interaction and feedback to specific questions submitted by the sponsor. FDA provides written feedback to the sponsor prior to the meeting and formal meeting minutes are also generated. Multiple pre-submission meetings are allowed and there are no FDA user fees associated with a pre-submission meeting.

NAMSA recommends a pre-submission at three time points during development of a PMA device including:
- Pre-Submission meeting to discuss pre-clinical testing (bench and animal)
- Pre-IDE meeting to discuss the human clinical study protocol
- Pre-PMA meeting to discuss the format and submission of the PMA

NAMSA can provide support throughout the pre-submission process and has extensive experience attending pre-submission meetings.
9.2 IDE Clinical Study
A clinical study performed in the United States must be conducted in accordance with FDA IDE regulations. The four chamber artificial heart will be designated a Significant Risk device, thus applications must be submitted and approved by both FDA and Institutional Review Boards prior to beginning any U.S. human studies.

Information to be included in an FDA IDE application includes: a description of the device (including all system components), its mechanism of action, device specifications (and drawings), bench testing, animal studies, biocompatibility studies, information regarding the manufacturing of devices, packaging and labeling and, the clinical study protocol that includes the patient informed consent, case report forms, list of investigational sites and investigators, and clinical risk/benefit.

FDA has 30 calendar days to provide feedback on the application although typically there are multiple rounds of questions and responses before FDA will give full approval. FDA’s policy is to not approve a clinical study design (pivotal) that they do not believe will provide valid scientific safety and effectiveness data to support the marketing application. FDA does not charge a fee for review of IDEs. All IDE studies must be registered in the Clinical Trials.gov database.

9.3 Premarket Approval Application
A Premarket Approval Application (PMA) will be required for the four chamber artificial heart and must contain the scientific and manufacturing information necessary to evaluate the safety and effectiveness of the device.

A PMA submission is required to contain device description and specification information, a discussion of alternative practices, marketing history, pre-clinical bench and animal testing, clinical study results and manufacturing information.

FDA will provide the sponsor with an initial response within 180 days of submission but there are typically multiple rounds of questions prior to approval.

It is expected that the four chamber artificial heart, as a “first-of-a-kind device” will be sent to an advisory panel for review and recommendation as part of the PMA process. A public meeting will be held to review the PMA and the advisory committee will vote on an approval recommendation. FDA takes into consideration the transcript of the meeting, the panel’s recommendation(s), and other information in reaching a final decision on the PMA. The criteria used by FDA to approve a PMA includes:

- reasonably assurance that a device is safe and effective
- valid scientific evidence that the probable benefits to health from the intended use of a device outweigh the probable risks
- the device will significantly help a large portion of the target population

Also, as part of the PMA approval process, the device manufacturing facility must pass an FDA facility inspection for compliance to the FDA Quality System Regulation.
9.4 Post-Approval Studies

FDA can impose requirements for post-approval studies at the time of approval of a PMA. The intent of post-approval studies is to evaluate device performance and potential problems when the device is used more widely than in clinical trials and over a longer period of time.

FDA will outline post-approval study requirements at the time of PMA approval and will typically specify the number of patients to be followed.

10. Quality System Development-Design Controls

Prior to placement of medical devices on the U.S. market, a company must have a documented quality system compliant to FDA’s Quality System Regulation (QSR) as defined in 21 CFR 820.

Design control requirements should be implemented early in the design and development process as FDA will review design records as part of the on-site facility inspection. Not all of the QSR requirements need to be established during the product development stages but most manufacturing and quality system controls should be in place before starting the clinical trial.

NAMSA can provide support in development of the Quality Management System.

11. Conclusion

The Four Chamber Redundant Impeller Artificial Heart technology is unique as compared to currently marketed heart assist devices. It will be considered a Class III high-risk device by FDA requiring an Investigational Device Exemption (IDE) and approval of a Premarket Approval Application (PMA) prior to placement on the U.S. market.

Extensive pre-clinical testing will be required prior to conducting the IDE human clinical study. Pre-clinical testing will include design verification testing, biological safety testing, software validation, electrical safety testing, usability and animal testing.

Human clinical testing protocols will require review and approval by FDA and Institutional Review Boards prior to starting clinical trials. The clinical testing should be conducted in phases beginning with a small feasibility safety study and then expanded into a larger pivotal study. After completion of successful clinical studies, a PMA submission will be required containing safety, efficacy and manufacturing information.

FDA will base their PMA approval decision on the following criteria:

- reasonably assurance that a device is safe and effective
- valid scientific evidence that the probable benefits to health from the intended use of a device outweigh the probable risks
- the device will significantly help a large portion of the target population

Additionally, as part of the PMA approval process, the device manufacturing facility must be compliant with the FDA Quality Management System regulation. It is recommended to implement design controls early in the development process and to have well developed quality systems in place prior to the IDE clinical study.

-- The following studies are proprietary and confidential --