SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Right Ventricular Assist Device
Device Trade Name:	Impella RP System
Device Procode:	OJE
Applicant's Name and Address:	ABIOMED, Inc. 22 Cherry Hill Drive Danvers, MA 01923
Date of Panel Recommendation:	None
Humanitarian Device Exemption (HDE) Number:	H140001
Humanitarian Use Device (HUD) Designation Number:	#12-0285
Date of HUD Designation:	July 13, 2012
Date of Notice of Approval to Applicant:	January 23, 2015

II. INDICATIONS FOR USE

The Impella RP System is indicated for providing circulatory assistance for up to 14 days in pediatric or adult patients with a body surface area ≥ 1.5 m^2 who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery.

The indications for use statement is identical to that which was granted for the HUD designation.

III. CONTRAINDICATIONS

The Impella RP System is contraindicated for patients with the following conditions:

- Disorders of the pulmonary artery wall that would preclude placement or correct positioning of the Impella RP device
- Mechanical valves, severe valvular stenosis or valvular regurgitation of the tricuspid or pulmonary valve
- Mural thrombus of the right atrium or vena cava
- Anatomic conditions precluding insertion of the pump
- Presence of a vena cava filter or caval interruption device, unless there is clear access from the femoral vein to the right atrium that is large enough to accommodate a 22 Fr catheter

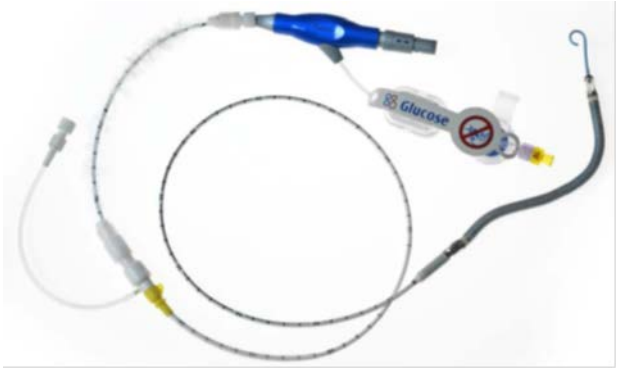
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Impella RP System labeling.

V. DEVICE DESCRIPTION

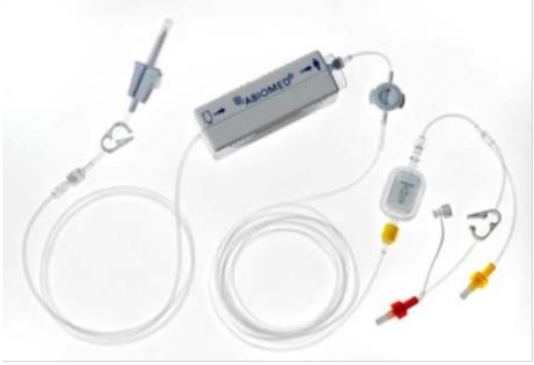
The Impella RP System is a minimally invasive, miniaturized percutaneous circulatory support system for the right ventricle. It is comprised of three components manufactured by ABIOMED, as shown in Figure 1:

- the Impella RP Catheter, a 22 Fr micro-axial flow pump catheter and its accessories
- the Automatic Impella Controller (AIC), a reusable extracorporeal drive console
- the Impella Purge Cassette, an infusion pump used to flush the Impella RP Catheter



(a) The Impella RP Catheter

(b) Automatic Impella Controller (AIC)



(c) The Impella Purge Cassette

Figure 1: The Impella RP System

The AIC controls both the Impella RP Catheter and the Impella Purge Cassette. It is a durable (reusable) driver. The Impella RP Catheter and the Purge Cassette are sterile, single use products. Both the AIC and the Impella Purge Cassette were 510(k) cleared (under K093801) for use with the Impella family of left heart circulatory support catheters.

During use, the Impella RP Catheter is percutaneously placed across the tricuspid and pulmonic valves via a single femoral venous access. It actively unloads the right ventricle by pumping blood from the inferior vena cava (IVC) into the pulmonary artery (PA), as

shown in Figure 2. The catheter is connected to the AIC, as shown in Figure 3. The AIC generates the signals required to power the drive motor of the catheter and provides the user interface. The AIC also incorporates the disposable Impella Purge Cassette purge system, which provides a pressure barrier to prevent blood from entering the catheter's drive motor. A dextrose (5-40% with 50 Units/ml of heparin added) solution is used as a purge fluid.

Two additional sterile, disposable accessories are kitted with the Impella RP Catheter to assist in its percutaneous insertion. These components are original equipment manufacturer (OEM) products, a 23 Fr Peel-away Introducer kit (Oscor Medical, cleared under K122084) and a 0.025" placement guidewire (Boston Scientific, cleared under K935997). Both OEM products are used within their cleared (i.e., general use) indications.

A reusable cart for the AIC is also provided, to allow ease of patient transport. In this regard, the AIC has been 510(k) cleared for use (i.e., with the cleared Impella left heart circulatory support catheters) by trained healthcare professionals during inter-hospital transport environments (i.e., via ambulance, helicopter or fixed-wing aircraft).

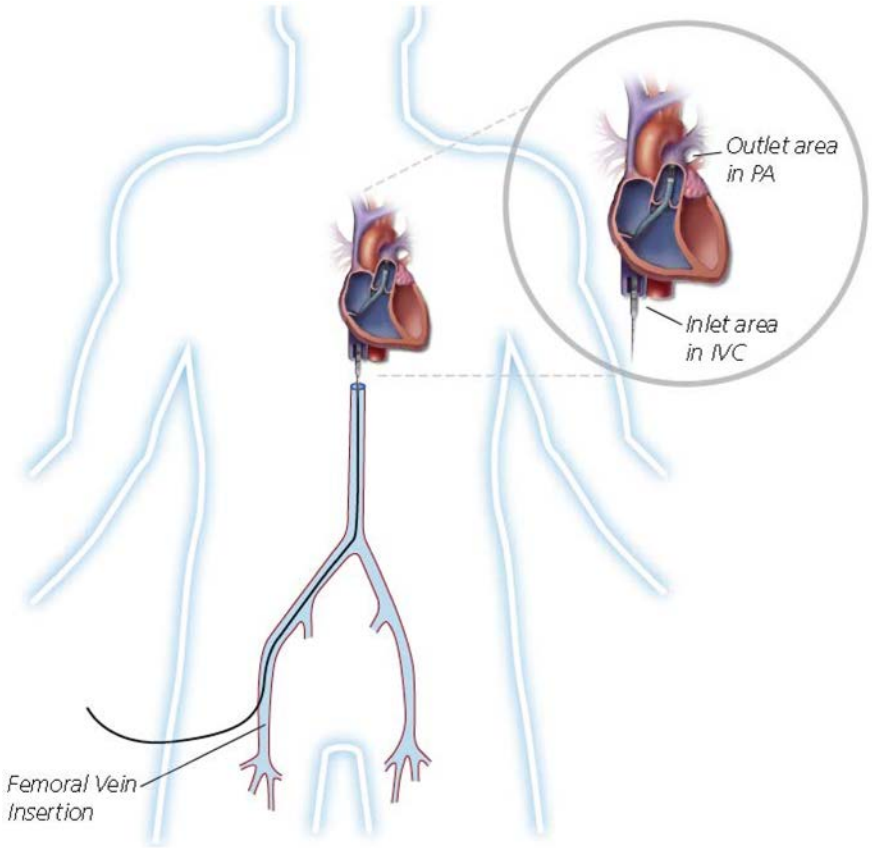


Figure 2: Impella RP Catheter placement during use

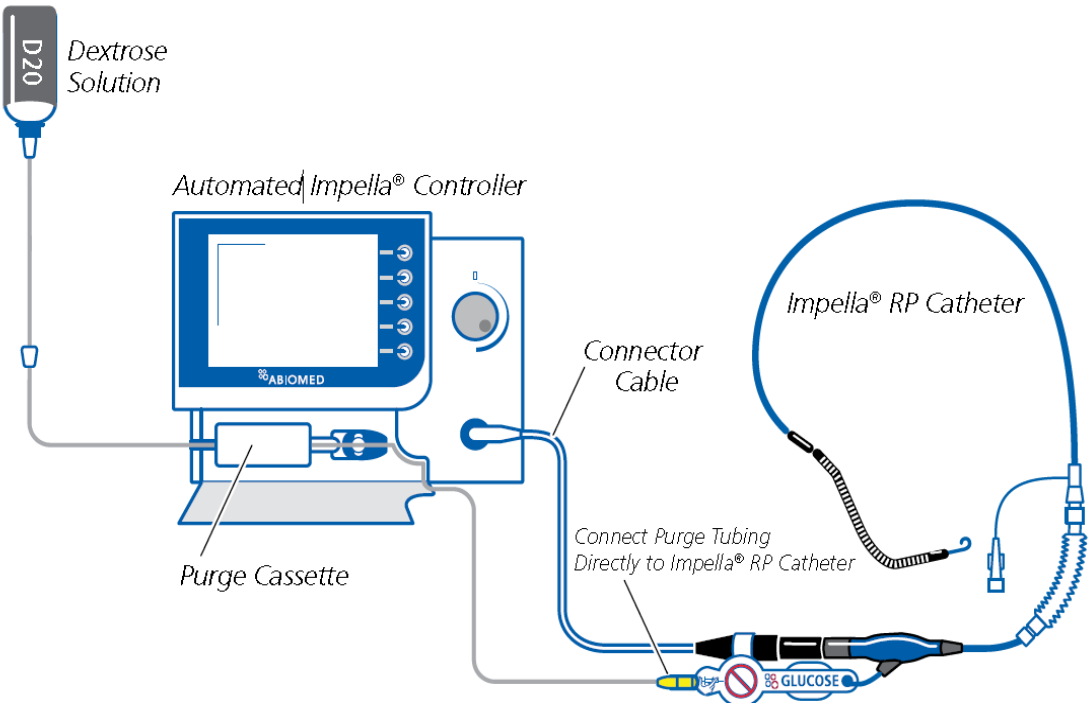


Figure 3: Clinical use set-up for the Impella RP System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of acute right heart failure include the following:

1. Inotropic support – The use of intravenous inotropic drugs in the setting of right ventricular failure (RVF) remains a common practice.

2. Surgical right ventricular assist devices (RVADs) – For severe temporary RVF, surgical RVADs have been used to stabilize the patient and recover the failing right ventricle. Three surgical ventricular assist devices have been approved for commercialization in the United States for right side support: the BVS5000/AB5000 VAD systems (ABIOMED, Inc.), the pVAD/IVAD systems (Thoratec, Inc.), and the CentriMag RVAD (Thoratec, Inc.).

VII. MARKETING HISTORY

The Impella RP System received a CE Mark for marketing in the Europe Union (EU) on April 4, 2014. It has been used in several of the EU member countries, including Germany, France and Belgium. It also has had limited clinical use in Canada, under Health Canada's Special Access Program. It has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Impella RP system:

- Arrhythmia
- Atrial fibrillation
- Bleeding
- Cardiac tamponade
- Cardiogenic shock
- Death
- Device Malfunction
- Hemolysis
- Hepatic failure
- Insertion site infection
- Perforation
- Phlegmasia cerulea dolens (a severe form of deep venous thrombosis)
- Pulmonary valve insufficiency
- Respiratory dysfunction
- Sepsis
- Thrombocytopenia
- Thrombotic vascular (non-central nervous system) complication
- Tricuspid valve injury
- Vascular injury
- Venous thrombosis
- Ventricular fibrillation and/or tachycardia

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Testing

In Vitro Verification Studies

In vitro verification studies were performed for the Impella RP System, including the Impella RP Catheter, the AIC, the Impella Purge Cassette, and the its disposable components. A list of the studies completed is provided in Table 1.

Table 1: *In vitro* verification studies completed with the Impella RP System

Test	Test Description	Applicable Standards or Acceptance Criteria	Results
Performance Testing			
Flow Characterization	To verify the flow calculation accuracy based on the correlation between the pressure (placement) signal and the blood flow through the pump	Total variance of ±0.4 L/Min between the averaged measured flow rate and the calculated flow rate over a differential pressure range of 0 - 140 mmHg.	Passed
Simulated Device Placement	To demonstrate the ability of the pump device to be placed using a peripheral catheter technique	- Insertion- Using a graded scale (1 (Easy) to 5 (Hard)), the mean evaluation grade for the pump insertion had to be ≤3 - Pushability/Torquability- Using the 1 to 5 graded scale, the mean evaluation grade for the push ability/torquability had to be ≤3	Passed
Sensor System Response	To demonstrate that the sensor was compatible for clinical use	The pressure sensor measures a reproducible waveform signal at 0.5 Hz and 3 Hz (mean amplitude ±4 mmHg).	Passed
Computational Fluid Dynamics	To demonstrate that the Impella RP rotor's flow field had acceptable shear forces and pressures during use	- Lowest static pressure is above level for cavitation in the pump. - Stress distribution of the fluid field shows that <1% (of fluid mass) is exposed to high stress.	Passed

Test	Test Description	Applicable Standards or Acceptance Criteria	Results
Computer Aided Anatomical Fit	To demonstrate that the Impella RP outflow cannula could be used with range of patient anatomies	Using CT scans and a computer fitting program, the 3D cannula configuration was shown to fit the expected range (BSA ≥ 1.5) of patient anatomies. A cadaver evaluation was also completed to validate the computer modeling.	Passed
Durability Testing			
Impella RP Durability	To demonstrate that the Impella RP design was consistent with 14 days of support in clinical use	The Impella RP must demonstrate a 14 day run reliability of 80% (at 80% confidence). The test ran for 2x this duration (28 days).	Passed
Bend Durability	To demonstrate that the Impella RP design was consistent with 14 days of simulated bending during clinical use	The Impella RP must demonstrate a 14 day simulated bend reliability of 80% (at 80% confidence). The test ran for 2x this duration (28 days).	Passed
Impella Purge Cassette Durability	To demonstrate that the Impella Purge Cassette was consistent with its clinical use with the Impella RP System	The Impella Purge Cassette must demonstrate a 14 day reliability of 80% (at 80% confidence).	Passed
Electromagnetic Compatibility Testing			
AIC with Impella RP Pump	To demonstrate that the Impella RP System complied with the applicable electrical standards	EN 60529, UL60601-1, IEC60601-1, EN60601-1 and CSA C22.2 NO 601.1-M90	Passed
Safety Testing			
Hemolysis	To demonstrate that the hemolysis generated by the Impella RP Catheter was acceptable	ASTM F1841-97(2005)	Passed
Biocompatibility- (Evaluation for Cytotoxicity, Sensitization, Intracutaneous Irritation, Systemic Toxicity, Genotoxicity, Hemocompatibility, Sub-chronic toxicity.)	To demonstrate biocompatibility of the Impella RP System	ISO 10993-1:2009	Passed
Packaging	To demonstrate that the packaging used for the Impella RP Catheter were acceptable	- EN 550 (SAL $>10^{-6}$) - The Impella RP packaging must demonstrate acceptable levels of bioburden, EtO residuals and pyrogens	Passed
Temperature	To demonstrate that the surface temperature of the Impella RP Catheter was acceptable	During operation at maximum flow, the Impella RP Catheter's surface temperature be ≤45°C.	Passed
Tensile	To demonstrate that the Impella RP's joint strengths were acceptable for use	EN ISO 10555	Passed
Corrosion	To demonstrate that the Impella RP Catheter's metal components would not corrode during use	DIN EN 10555-1	Passed
Tightness	To demonstrate that the Impella RP Catheter's internal purge line had an acceptable functional reliability	Following the bending durability test (see above), the internal purge lines of the Impella RP Catheter must be not leak (at 1800 mmHg).	Passed

Software Verification and Validation

Software design and testing was conducted in accordance with FDA guidance document entitled "Guidance for Industry and FDA Staff - Guidance for the Content of Pre-market Submissions for SW Contained in Medical Devices" (issued on May 11, 2005). The software development process also complies with IEC 60601-1-4:1996. Verification and validation testing was performed using the latest software version. The verification test results demonstrated that all of the software requirements for the AIC were met. The validation test results demonstrated that the Impella RP System performed as intended.

B. Animal Studies

Two animal studies were completed with the Impella RP System, as listed in Table 2.

Table 2: Animal studies completed with the Impella RP System

GLP Animal – Acute		
Report	**Test Type – Description**	**Test Result**
Insertion and Feasibility	Verification- *in vivo* (porcine, N=6) study to demonstrate ease of device insertion and hemodynamic improvement (in an acute failing heart model).	Passed
GLP Animal - Chronic		
Report	**Test Type – Description**	**Test Result**
Safety and Simulated Use (14 days)	Verification- *in vivo* (bovine n=6) study to demonstrate device safety for 14 days of use.	Passed

C. Sterilization

The Impella RP Catheter and the Impella Purge Cassette are both sterilized. The sterilization method is 100% ethylene oxide (EO), and the sterilization process is validated to provide a sterility assurance level (SAL) of 10^{-6} in accordance with international standards for sterilization processes for medical devices, ANSI/AAMI/ISO 11135-1:2007, ANSI/AAMI/ISO 14937:2009 and EN 550:1994. A validated post-sterilization aeration process assures that residual levels of EO and ECH (ethylene chlorohydrin) are within acceptable limits specified by ANSI/AAMI/ISO 10993-7:2008.

D. Package Integrity and Shelf Life

Package integrity testing was completed for each of the Impella RP System components. Summaries of the tests completed are provided in Table 3.

Table 3: Summary of Impella RP System package integrity testing

Test	Description	Test Result
Package Test: Seal Strength and Integrity – Impella RP	This test verified that the Impella RP package seals have acceptable: 1) strength (tensile test) 2) integrity (dye penetration test)	Passed
Package Test: Shipping- Impella RP	This test verified that that the Impella RP packaging will provide adequate protection for shipment (ISTA 2A Standard).	Passed
Package Test: Shipping & Transport- AIC	This test verified that the AIC packaging will provide adequate protection for shipment. (ISTA 2A Standard).	Passed
Package Tests: Seal Strength & Integrity- Impella Purge Cassette	This test verified that the Impella Purge Cassette's package seals have acceptable: 1) strength (tensile test), 2) integrity (dye penetration test)	Passed
Package Test: Shipping- Impella Purge Cassette	This test verified that that the Impella Purge Cassette's packaging will provide adequate protection for shipment (ISTA 2A Standard).	Passed

The shelf life for the Impella RP Catheter and Impella Purge Cassette is established to be 2 years.

X. SUMMARY OF CLINICAL INFORMATION

A. Pivotal Clinical Study Design

The pivotal study, RECOVER RIGHT, was a prospective, multi-center, non-randomized study conducted under IDE G120159. The primary objective for the study was to assess safety and effectiveness of the use of the Impella RP device in patients with RVF refractory to medical treatment who require hemodynamic support.

The primary endpoint was the survival rate at 30 days post device explant or hospital discharge (whichever is longer), or at induction of anesthesia for a longer term therapy, including heart transplant or implant of a surgical RVAD (as a bridge-to-recovery or bridge-to-transplant).

The secondary effectiveness endpoint was determined by the following:

- Central venous pressure (CVP) and cardiac index (CI) improvement post initiation of Impella RP support
- Decreased use of inotropes during support
- Improvement in left ventricular assist device (LVAD) flow or left ventricle pumping function secondary to the increased venous return by the Impella RP within 48 hours post implant

The secondary safety endpoint was determined by the rates of the following adverse events at 30 days or discharge (whichever is longer), or at induction of anesthesia for a longer term therapy, including heart transplant or implant of a surgical RVAD (as a bridge-to-recovery or bridge-to-transplant):

- Death (any cause of death and cardiac death)
- Major bleeding
- Hemolysis
- Pulmonary embolism
- Tricuspid/pulmonary valve dysfunction (defined as tricuspid/pulmonic valve injury resulting in increased valve regurgitation versus baseline)

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Patients who have developed signs of RVF either a) within 48 hours post-implantation of an FDA approved implantable surgical LVAD (Cohort A) or b) subsequent to post-cardiotomy cardiogenic shock within 48 hours post surgery or post myocardial infarction (Cohort B).

   RVF was defined as a CI <2.2 l/min/m^2 despite continuous infusion of high dose of inotropes (defined as Dobutamine of ≥10μg/kg/min or equivalent for more than 15 minutes (120 minutes for milrinone) and/or administration of more than one inotrope/vasopressor medication) and any of the following:
   - CVP >15 mmHg
   - CVP/Pulmonary Capillary Wedge Pressure (PCWP) or Left Atrial Pressure (LAP) >0.63
   - Moderate to severe global RV dysfunction on echocardiography defined as one of the following criteria: global RV hypokinesis, a TAPSE score of

≤14 mm, right ventricular diameter at base >42mm, right ventricular short axis (or mid cavity) diameter >35mm

2. Age ≥18 years old
3. Signed informed consent

Exclusion Criteria

Cohort A

1. INTERMACS 1 patients (Critical cardiogenic shock patient who is "crashing and burning," has life-threatening hypotension and rapidly escalating inotropic or pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels)
2. End organ failure (defined as hepatic total bilirubin ≥ 5 mg/dL based on lab data within 24 hours prior to Impella RP initiation, renal: creatinine ≥ 4 mg/dL based on lab data within the 24 hours prior to Impella RP initiation)
3. Evidence of acute neurologic injury following LVAD implant
4. Active infection defined as two of the following White Blood Cells Count (WBC)>12,500, positive blood culture, fever
5. Right Atrium (RA), Right Ventricle (RV) and/or Pulmonary Artery (PA) thrombus
6. Prosthetic valves in the right heart (tricuspid or pulmonary valves)
7. Structural tricuspid valve disease
8. Unrepaired atrial septal defect/patent foramen ovale
9. Severe pulmonary valve stenosis or insufficiency
10. Intolerance to anticoagulant or antiplatelet therapies
11. Severe pulmonary hypertension (systolic Pulmonary Artery Pressure, PAPs>60mmHg)
12. Documented Deep Vein Thrombosis (DVT) and/or presence of Inferior Vena Cava (IVC) filter
13. Anatomic conditions precluding insertion of the pump or safe use of the device such as severe anomaly of the inferior vena cava, calcification or other disorders of the pulmonary artery wall
14. Pulmonary artery conduit replacement
15. Patients on right side support device or extracorporeal membrane oxygenation
16. Current diagnosis of pulmonary embolism
17. Patient with anatomic anomalies or aortic diseases like aortic dissection, Marfan-Syndrome, Morbus Erdheim-Gsell or others
18. Allergy or intolerance to contrast media
19. Thrombolysis within the previous 30 days or known existing coagulopathy such as thrombocytopenia, heparin induced thrombocytopenia (HIT), hemoglobin diseases such as sickle cell anemia or thalassemia
20. Existing congenital heart disease that would preclude the insertion of the device
21. Participation in any other clinical investigation that is likely to confound study results or affect study outcome

Cohort B

1. Patient in profound cardiogenic shock defined as systolic blood pressure < 75 mmHg and CI <1.3 l/min/m2 despite 2 or more high dose of inotropes ± mechanical support or evidence of shock-related end-organ damage, metabolic acidosis (pH 7.1 or less) and not corrected by 100 ml $NaHCO_3$ (1mEq/ml), disseminated

intravascular coagulation or clinical evidence of diffuse brain injury or in cardiogenic shock for >24 hours
2. Acute myocardial infarction (AMI) with mechanical complications (ventricular septal defect, myocardial rupture, papillary muscle rupture)
3. Unsuccessful revascularization of the Right Coronary Artery (RCA) defined as Thrombolysis in Myocardial Infarction (TIMI) flow 0.1 post Percutaneous Coronary Intervention (PCI) or unsuccessful coronary bypass
4. Active infection defined as two of the following WBC>12,500, positive blood culture, fever
5. RA, RV and/or PA thrombus
6. Prosthetic valves in the right heart (tricuspid or pulmonary valves)
7. Unrepaired atrial septal defect/patent foramen ovale
8. Structural tricuspid valve disease
9. Severe pulmonary valve stenosis or insufficiency
10. Intolerance to anticoagulant or antiplatelet therapies
11. Severe pulmonary hypertension (PAP>60mmHg)
12. Documented DVT and/or presence of IVC filter
13. Anatomic conditions precluding insertion of the pump or safe use of the device such as severe anomaly of the inferior vena cava, calcification or other disorders of the pulmonary artery wall
14. Pulmonary artery conduit replacement
15. Patient on right side support device or extracorporeal membrane oxygenation.
16. Current diagnosis of pulmonary embolism
17. Patient with aortic diseases like aortic dissection, Marfan-Syndrome, Morbus Erdheim-Gsell or others
18. Allergy or intolerance to contrast media
19. Thrombolysis within the previous 30 days or known existing coagulopathy such as thrombocytopenia, heparin induced thrombocytopenia (HIT), hemoglobin diseases such as sickle cell anemia or thalassemia
20. Existing congenital heart disease that would preclude the insertion of the device
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Study Organization

ABIOMED handled site management, site monitoring, data management and oversight of safety processes, including the Executive Steering Committee, the Physician Medical Monitor, and the Clinical Events Committee (CEC). The study also included an independent Echocardiography Core Laboratory (Duke Clinical Research Institute, Raleigh NC) that provided imaging protocol design, mandatory echocardiography training and certification for each trial site, image management, and image analyses. A cardiothoracic surgeon was selected as the Physician Medical Monitor, who was charged with reviewing study data in order to protect the safety and well-being of human research subjects and the scientific integrity of the investigation. The independent CEC was organized through Harvard Clinical Research Institute (HCRI) and comprised physicians from the fields of interventional cardiology, heart failure and cardiac surgery who were experienced with the safety issues specific to mechanical circulatory support. The CEC members reviewed all clinical data associated with the events, adjudicated the events and determined whether a causal relationship to the investigational device or the procedure existed.

Statistical Considerations

Considering the low incidence of RVF and challenges to enroll patients in a reasonable time frame, the study was not designed to be hypothesis driven. Data were described as mean ± standard deviation (mean ± SD).

B. Accountability of HDE Cohort

A total of 30 subjects were enrolled into the study. Of these 30 subjects, there were 18 subjects (60%) enrolled in Cohort A and 12 subjects (40%) enrolled in Cohort B. Details are shown in Figure 4.

C. Study Population Demographics and Baseline Characteristics

The patient baseline characteristics are summarized in Table 4. The overall age was 59±15 years old. Among all patients, 88.5% presented with congestive heart failure (CHF), 60% had history of arrhythmia, 57% had ICD or pacemaker implanted, 53% had diabetes, 37.5% had chronic kidney disease, and 20% had prior CVA. Of note, 60% of the patients had received blood products and 78.6% were in NYHA class IV prior to device implant.

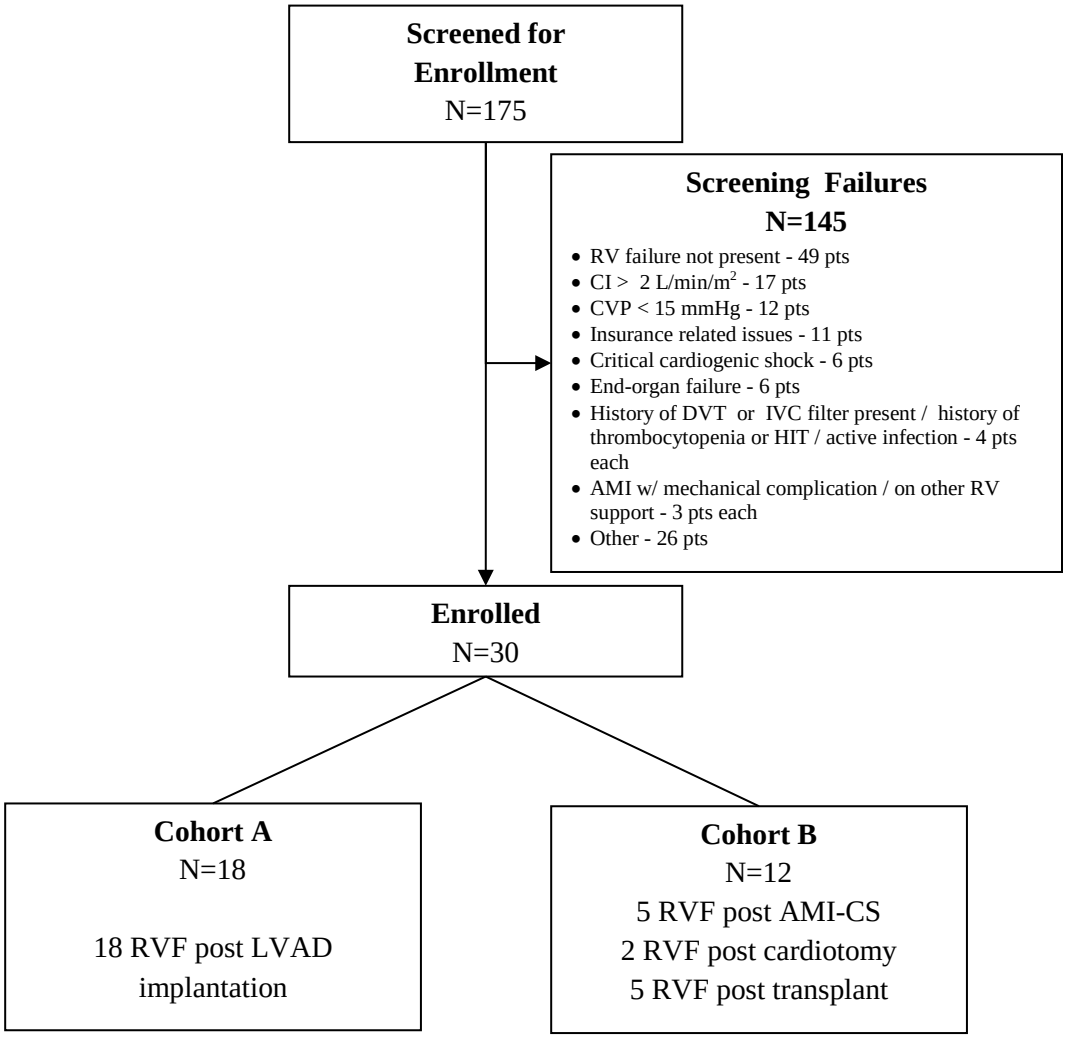

Figure 4: Study flow schematic

Table 4: Patient characteristics

Patient Characteristic	All Patients (N=30)	Cohort A (N=18)	Cohort B (N=12)
Age			
Mean±SD (N)	59.2±15.2 (30)	55.8±13.9 (18)	64.3±16.2 (12)
Gender			
Male	76.7% (23/30)	83.3% (15/18)	66.7% (8/12)
Female	23.3% (7/30)	16.7% (3/18)	33.3% (4/12)
Race			
White	53.3% (16/30)	55.6% (10/18)	50.0% (6/12)
Black or African American	40.0% (12/30)	38.9% (7/18)	41.7% (5/12)
Asian	6.7% (2/30)	5.6% (1/18)	8.3% (1/12)
Body Surface Area (m^2)			
Mean±SD (N)	1.94±0.22 (30)	2.01±0.23 (18)	1.85±0.18 (12)
Hypertension	80.0% (24/30)	77.8% (14/18)	83.3% (10/12)
Coronary Artery Disease	66.7% (20/30)	66.7% (12/18)	66.7% (8/12)
Congenital Heart Disease	12.5% (3/24)	6.7% (1/15)	22.2% (2/9)
Congestive Heart Failure	88.5% (23/26)	100.0% (18/18)	62.5% (5/8)
NYHA Classification			
I	3.6% (1/28)	0.0% (0/18)	10.0% (1/10)
II	3.6% (1/28)	5.6% (1/18)	0.0% (0/10)
III	14.3% (4/28)	16.7% (3/18)	10.0% (1/10)
IV	78.6% (22/28)	77.8% (14/18)	80% (8/10)
Myocardial Infarction	46.7% (14/30)	50.0% (9/18)	41.7% (5/12)
PCI	46.7% (14/30)	50.0% (9/18)	41.7% (5/12)
CABG	13.3% (4/30)	5.6% (1/18)	25.0% (3/12)
Arrhythmia	60.0% (18/30)	66.7% (12/18)	50.0% (6/12)
Cerebrovascular Accident	16.7% (5/30)	5.6% (1/18)	33.3% (4/12)
Stroke	20.0% (1/5)	0.0% (0/1)	25.0% (1/4)
TIA	60.0% (3/5)	0.0% (0/1)	75.0% (3/4)
Smoking	44.8% (13/29)	52.9% (9/17)	33.3% (4/12)
Chronic Obstructive Pulmonary Disease	12.0% (3/25)	16.7% (3/16)	0.0% (0/9)
Diabetes	53.3% (16/30)	61.1% (11/18)	41.7% (5/12)
Chronic Kidney Disease	37.5% (9/24)	37.5% (6/16)	37.5% (3/8)
Subject is On Dialysis	0.0% (0/9)	0.0% (0/6)	0.0% (0/3)
History of LVAD Implantation	16.7% (5/30)	0.0% (0/18)	41.7% (5/12)
HeartMate (Thoratec)	40.0% (2/5)	N/A	40.0% (2/5)
Heartware HVAD	40.0% (2/5)	N/A	40.0% (2/5)
Other	20.0% (1/5)	N/A	20.0% (1/5)
Valve Replacement/Repair	16.7% (5/30)	16.7% (3/18)	16.7% (2/12)
ICD/Pacemaker Implanted	56.7% (17/30)	72.2% (13/18)	33.3% (4/12)
Subject received any blood products within the past 48 hours			
% Received	60.0% (18/30)	61.1% (11/18)	58.3% (7/12)
LVEF (%)			
Mean±SD (N)	22.6±16.66 (24)	14.1±7.35 (16)	39.6±17.3 (8)
TAPSE (mm)			
Mean±SD (N)	8.9±4.7 (16)	8.1±4.2 (10)	10.3±5.5 (6)

Baseline laboratory parameters are provided in Table 5. The test results were similar between the two cohorts. Overall, patients presented with signs of tissue hypoperfusion and end-organ dysfunction at the time of implant as demonstrated by the elevated creatinine, bilirubin and lactate dehydrogenase.

Table 5: Baseline laboratory parameters

Baseline Characteristics	All Patients Mean±SD (N)	Cohort A Mean±SD (N)	Cohort B Mean±SD (N)
WBC count (10^3)	11.80±6.38 (30)	11.47±7.28 (18)	12.31±5.01 (12)
Platelets count (10^3)	204.09±87.24 (30)	191.76±75.24 (18)	222.58±103.42 (12)
Hemoglobin (g/dL)	10.31±2.01 (30)	10.09±1.79 (18)	10.63±2.35 (12)
Hematocrit (%)(N)	31.40±5.84 (30)	30.84±5.41 (18)	32.24±6.58 (12)
Plasma Free Hemoglobin (mg/dL)	26.22±50.90 (16)	12.42±11.32 (11)	56.58±87.86 (5)
BUN (mg/dL)	24.98±13.47 (30)	23.58±13.19 (18)	27.08±14.19 (12)
Serum Creatinine (mg/dL)	1.40±0.60 (30)	1.37±0.57 (18)	1.43±0.65 (12)
Creatinine Clearance (mL/min)	62.82±25.33 (19)	68.40±26.73 (12)	53.26±21.12 (7)
Total Bilirubin (mg/dL)	1.27±0.84 (29)	1.46±1.04 (17)	0.99±0.32 (12)
LDH (U/L)	441.73±315.57 (21)	452.33±344.74 (15)	415.22±253.73 (6)
BNP (pg/mL)	3867±8483 (16)	1480±2125 (9)	6937±12423 (7)

WBC: White Blood Cells; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; BNP: B-type natriuretic peptide

D. Procedural, Support and Hemodynamic Characteristics

Patients' procedural and support characteristics are presented in Table 6. Percutaneous placement of the device was attempted through right femoral vein in 96.7% (29 out of 30) of cases and through the left femoral vein in 3.3 % (1 out of 30) of cases. There was minimal blood loss during introducer and catheter placement with less than 25 mL of blood loss recorded in 89.3% and 60.7% of patients, respectively. The average duration of support with the Impella RP was 3 days for the entire population (ranging from 13 hours to 8 days) and was similar between the two cohorts. The pump flow on support was 3.23±0.35 L (ranging 2.5-4.0 L/min).

Table 6: Procedural characteristics

Procedural Characteristic	All Patients	Cohort A	Cohort B
Side of Implantation			
Left Femoral Vein	3.3% (1/30)	0.0% (0/18)	8.3% (1/12)
Right Femoral Vein	96.7% (29/30)	100.0% (18/18)	91.7% (11/12)
Estimated Blood Loss during Introducer Insertion			
<25mL	89.3% (25/28)	93.8% (15/16)	83.3% (10/12)
25-50 mL	3.6% (1/28)	0.0% (0/16)	8.3% (1/12)
>100 mL	7.1% (2/28)	6.3% (1/16)	8.3% (1/12)
Estimated Blood Loss during Catheter Placement			
<25mL	60.7% (17/28)	68.8% (11/16)	50.0% (6/12)
25-50 mL	32.1% (9/28)	25.0% (4/16)	41.7% (5/12)
>100 mL	7.1% (2/28)	6.3% (1/16)	8.3% (1/12)
Duration of Support (hours)			
Mean±SD (N)	73.15±37.04 (27)	76.73±31.64 (15)	68.66±43.92 (12)
Average device flow (L/min)			
Mean±SD (N)	3.23±0.35 (27)	3.14±0.39 (16)	3.35±0.26 (11)

The hemodynamic characteristics are provided in Table 7. All patients presented with RVF and poor hemodynamics at the time of implant, despite high dose of inotropes/pressors. The hemodynamic profile was consistent between the two cohorts.

Table 7: Baseline support and hemodynamic characteristics

Hemodynamic Characteristics	All Patients Mean±SD (N)	Cohort A Mean±SD (N)	Cohort B Mean±SD (N)
Number of inotropes/pressors (Prior to device Insertion	3.23±1.14 (30)	3.56±1.10 (18)	2.75±1.06 (12)
Hemodynamics (Prior to device Insertion)			
Cardiac Index (L/min/m^2)	1.82±0.23 (30)	1.84±0.23 (18)	1.80±0.23 (12)
Cardiac Output (L/min)	3.81±1.13 (28)	4.17±1.32 (16)	3.34±0.60 (12)
Pulmonary Capillary Wedge Pressure (PCWP)/ Left Arterial Pressure (LAP) (mmHg)	17.44±7.28 (16)	14.50±4.60 (8)	20.38±8.53 (8)
Right Arterial Pressure (RAP)/Central Venous Pressure (CVP) (mmHg)	19.23±3.91 (30)	19.25±4.36 (18)	19.21±3.31 (12)
PAP Systolic (mmHg)	40.38±12.10 (29)	41.50±13.87 (18)	38.55±8.78 (11)
PAP Diastolic (mmHg)	20.21±8.62 (29)	21.33±9.16 (18)	18.36±7.70 (11)
Mean Arterial Pressure (MAP) (mmHg)	70.46±14.32 (21)	74.08±10.93 (13)	64.59±17.81 (8)
Heart Rate (BPM)	90.21±20.49 (28)	91.71±22.69 (17)	87.91±17.34 (11)
LVAD Flow (L/min) (Cohort A only)	3.96±0.64 (17)	3.96±0.64 (17)	N/A

E. Primary Endpoint Results

The primary endpoint of survival at 30 days or discharge post device removal (whichever is longer), or to induction of anesthesia for the next longer-term therapy was achieved in 73% of the study population, with 83% in cohort A and 58% in cohort B. Patient outcomes are presented in Table 8.

Table 8: Patient outcome

Event	All Patients	Cohort A (N=18)	Cohort B (N=12)
Alive @ 30 days % (n)	73 % (22/30)	83.3% (15/18)	58.3% (7/12)
Alive @ Discharge % (n)	70 % (21/30)	77.8% (14/18)	58.3% (7/12)
Alive at 30day/DC/next therapy %(n)	73 % (22/30)	83.3% (15/18)	58.3% (7/12)

F. Secondary Safety Endpoint Results

The secondary safety endpoint results are provided in Table 9.

Table 9: Secondary safety endpoints

Safety Endpoints	All Patients (N=30)	Cohort A (N=18)	Cohort B (N=12)
Death	26.7% (8/30)	16.7% (3/18)	41.7% (5/12)
Major Bleeding	60.0% (18/30)	55.6% (10/18)	66.7% (8/12)
Hemolysis	13.3% (4/30)	16.7% (3/18)	8.3% (1/12)
Pulmonary Embolism	0.0% (0/30)	0.0% (0/18)	0.0% (0/12)
Tricuspid & Pulmonary Valve Dysfunction*	3.3% (1/30)	5.6% (1/18)	0.0% (0/12)

** based on echocardiographic core lab analysis*

Major bleeding events, though numerically high (18/30, 60% of patients), were predominantly related to the surgical procedure with post-cardiotomy surgical bleeding accounting for 83% (15/18: LVAD implantation n=10, Cohort A; or heart transplant or valve replacement surgery n=5, Cohort B) of major bleeding events. The post-cardiotomy patients had complex surgical interventions with administration of blood

products. Following these procedures, the chest was often left open and the patients required repeated wash-outs and surgical exploration to control bleeding prior to chest closure. Post surgical coagulopathy and need for blood products also contributed to these events. Bleeding events that were potentially device related were low (3/18 in Cohort B, 1/3 at access site). Overall, the amount of bleeding during insertion of the device was also low for the combined introducer sheath placement and the Impella RP catheter insertion. Ninety-three percent (93%) of the patients lost less than 100 mL of blood

G. Secondary Effectiveness Endpoint Results

CVP and CI improvement post initiation of Impella RP support

The hemodynamics improved in the first 24 hours of support when compared with pre-implant in the overall patient population as seen in Figure 5. The CI improved from 1.82±0.04 to 3.3±0.23 L/min/m^2. The CVP decreased from 19.2±0.7 to 12.6±1 mmHg.

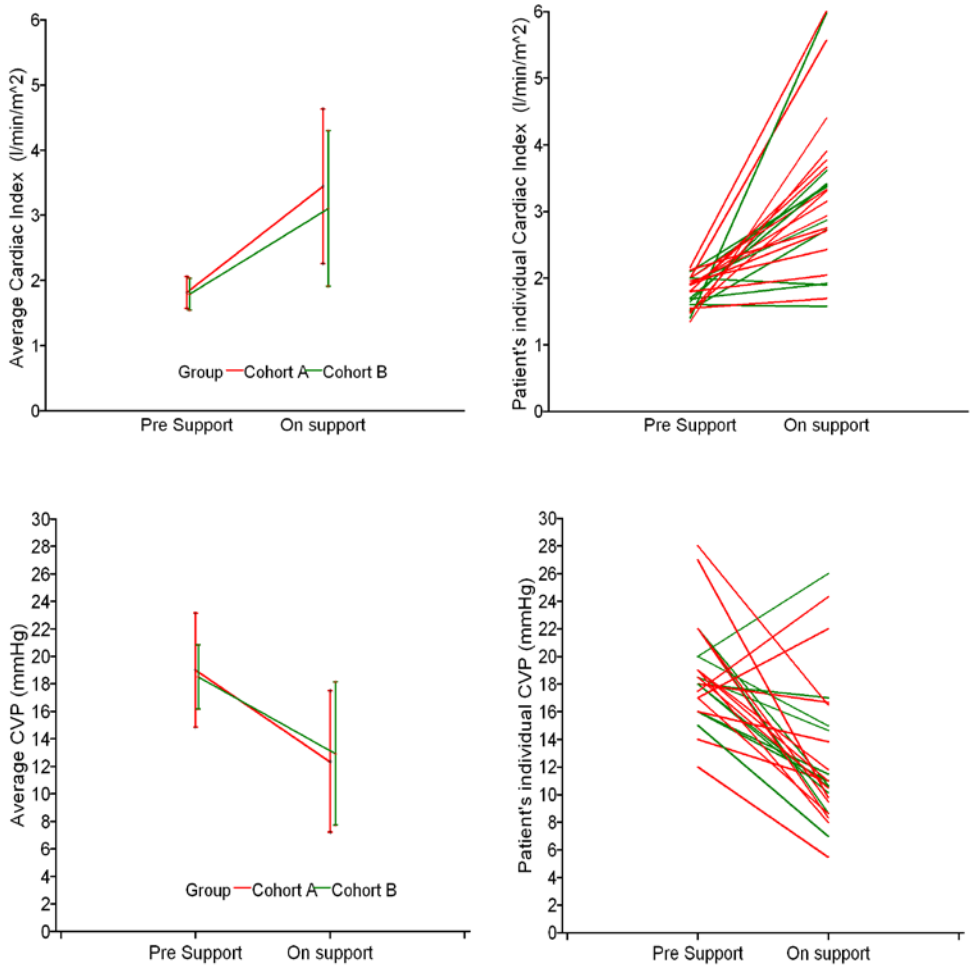

Figure 5: Cardiac index (CI) and central venous pressure (CVP) measured during the study

Improvement in LVAD flow or LV pumping function

The LVAD flow in Cohort A patients improved after the initiation of Impella RP from 3.96±0.16 L/min to 4.62±0.14 L/min, as depicted in Figure 6.

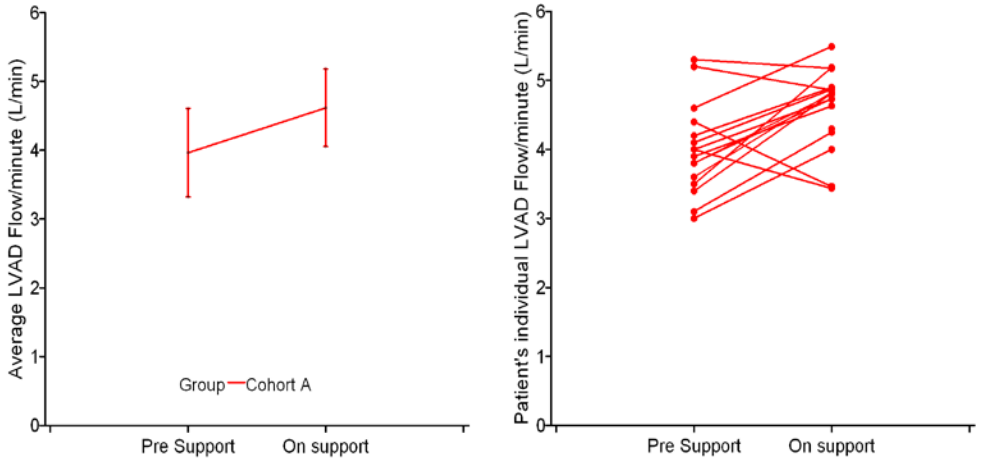

Figure 6: LVAD flow changes from baseline to on-support

In conclusion, the use of the Impella RP device improved patient hemodynamics while providing ventricular unloading in the combined cohorts. The level of support was sufficient to restore the hemodynamics of these sick patients to a normal range.

Decreased use of inotropes during support

The use of inotropes showed an initial increase on support then generally trended down over time during and after Impella RP support, as shown in Figure 7.

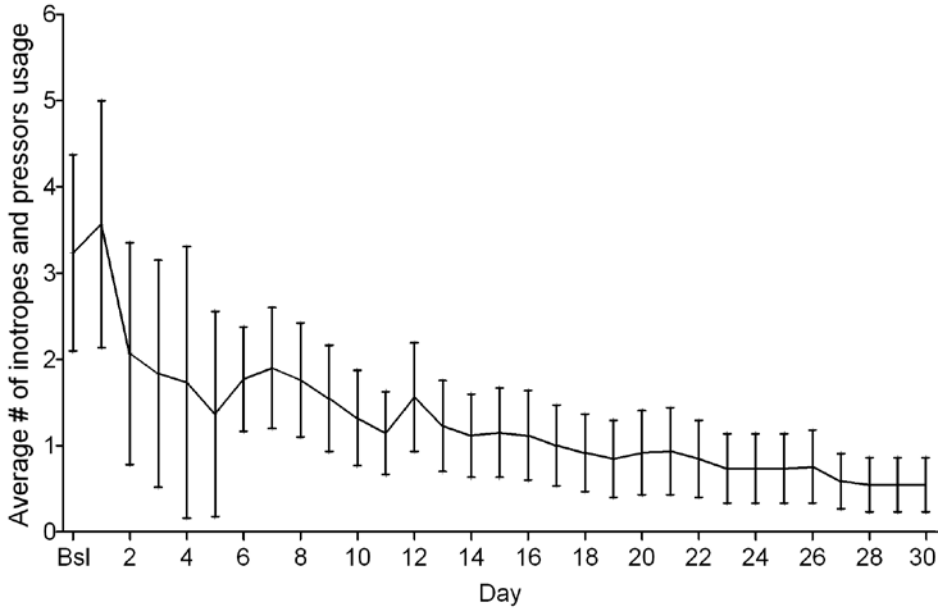

Figure 7: Use of inotropes during and after Impella RP support

H. Other Relevant Clinical Findings

Safety

- *Vascular complications:* There were no reported vascular complications in the venous system related to use of the large bore sheath provided with the Impella RP pump.

- *Integrity of Cardiac and Valvular Structures:* A comprehensive echocardiographic safety analysis on echocardiographic images acquired at different time points before, during and after Impella RP support performed by the Echocardiography Core Laboratory showed no evidence of any structural damage to the right ventricular chamber, tricuspid or pulmonary valves, or cordae or papillary muscles.

Effectiveness

- *Right Ventricular Function:* There were 21 patients who had paired echocardiographic images for analysis of right ventricular function. The majority of these patients showed global (versus regional) dysfunction prior to use of the Impella RP device. In 90% of the patients (19/21), there was either an improvement or maintenance of right ventricular function post device placement, as shown in Figure 8.

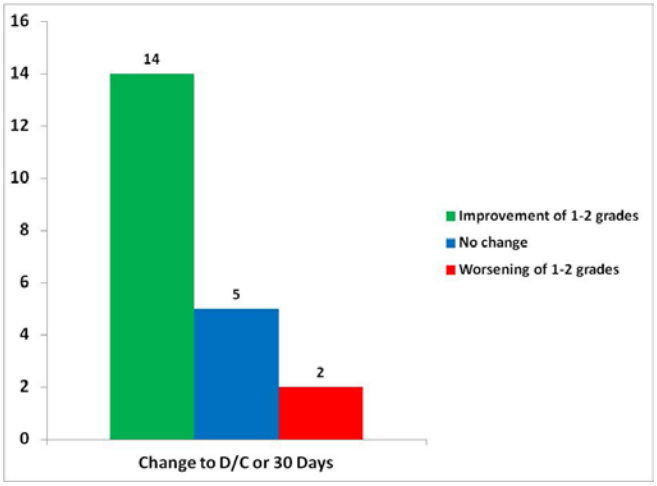

Figure 8: Right ventricular function changes from baseline to 30 days or discharge

- *Duration of support:* The duration of support with the Impella RP was 3.05±1.5 days.

Gender Analysis

The outcomes by gender were also examined. A trend towards higher complications and mortality was observed in female patients; however, the small sample size and the multiple cohorts studied prevent any conclusions based on gender.

Device Malfunctions

During the RECOVER RIGHT trial, the clinical investigators reported seven (7) device malfunctions in 7 different patients: 5 were related to the Impella RP pump, one to the AIC and one to the off the shelf introducer sheath. Only one affected patient had a device related Adverse Event (AE). In this case, the AE was related to the initial insertion of the Impella RP pump, which ultimately was successfully delivered for support. The device malfunction for this patient was a pump stop secondary to a complete cessation of anti-

coagulation therapy (including the use of heparin in the purge fluid for the pump). This is a known failure mode for the micro-axial pump design, which requires anti-coagulation therapy (including a continuous flush of purge fluid containing heparin through the pump motor).

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 12 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. RISK AND PROBABLE BENEFIT ANALYSIS

A. Safety Conclusions

The nature and types of risks associated with the Impella RP System are consistent with those expected in the device treatment of this very ill patient population. Successful percutaneous insertion was achieved in 97% of the patients. The number of device related AEs was low.

B. Effectiveness Conclusions

In the cohorts studied, use of the Impella RP System to provide percutaneous hemodynamic support for right heart failure had a high survival rate. The 30-day survival rate in the 30 patients treated with the Impella RP System was 73%, a substantial improvement over expected survival for medically treated patients. Additional benefits relating to supplementation of right heart output, hemodynamic stability, unloading of the RV, and RV recovery or bridge to another therapy were seen in this small trial. Percutaneous insertion and removal allowed by the Impella RP design resulted in a very low incidence of bleeding and vascular complications. Support durations were relatively short, ranging from 13 hours to 8 days.

C. Benefit-Risk Conclusions

The positive survival and hemodynamic benefits associated with use of the Impella RP System, combined with the acceptable incidence of adverse events for the patient population being treated, suggest the probable benefits of Impella RP use in the treatment of acute right or decompensation heart failure outweigh its risks. This benefit-risk determination is also acceptable when taking into account the risks and probable benefits associated with alternative device therapies and the high morbidity and mortality associated with right heart failure, if left untreated.

D. Overall Conclusions

RECOVER RIGHT was the first study of a percutaneous RVAD in patients with RVF refractory to medical treatment who had very limited therapeutic options. In the studied

patient population, the use of the Impella RP device provided adequate circulatory support to reverse shock and to restore normal hemodynamic parameters, and achieved an overall survival rate of 73% at 30 days or discharge (whichever is longer) or to a long term therapy. The Impella RP device had a reasonable overall safety profile, with reliable percutaneous insertion and a low incidence of bleeding and vascular complications.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee because other marketing applications for ventricular assist devices have been reviewed by the panel. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Impella RP System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on January 23, 2015.

The final conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies (PAS) as described below:

1. *Impella RP Prospective Study*: This study will be conducted as per protocol dated October 17, 2014, version 1.0 received via interactive email on November 25, 2015. This study will be conducted to monitor the postmarket safety and effectiveness of the Impella RP device. This will be a single-arm multicenter study of patients with right ventricular failure in need of hemodynamic support. Patients will be followed at 30 and 180 days post device explant.

   A sample size of 30 consecutive patients will be enrolled from up to 15 US sites. The patient population will be similar to the RECOVER RIGHT IDE study population.

   The primary safety endpoint of survival at 30 days post device explant or hospital discharge (whichever is longer), or to induction of anesthesia to a longer term therapy, which includes a heart transplant or an implant of a surgical RVAD, will be descriptively reported.

   The secondary safety endpoints are major adverse events at hospital discharge or to induction of anesthesia to a longer term therapy, including death (any cause of

death and cardiac death), major bleeding, hemolysis, pulmonary embolism. The secondary effectiveness endpoint of improvement in hemodynamic parameters (cardiac index, central venous pressure and LVAD flows) will be assessed after initiation of Impella RP support. Survival only will be evaluated at 30 days and 180 days post device explant. All secondary endpoints will be descriptively reported.

2. *Impella RP Pediatric Study:* This study will be conducted as per protocol dated November 10, 2014, version 1.0 received via interactive email on November 25, 2014 to monitor postmarket safety and effectiveness of the Impella RP device in pediatric patients. This will be a single-arm multicenter study of pediatric patients under 18 years of age with BSA $\geq 1.5 m^2$ who developed right ventricular failure and were supported with the Impella RP device. The patient data at baseline and from implant through 180 days post device explant will be retrospectively collected.

   A total of 15 consecutive pediatric patients or all pediatric patients supported with the Impella RP over a 5-year period (whichever comes first) will be enrolled in the study at a minimum of 5 participating clinical centers.

   The primary safety endpoint of survival at 30 days post device explant or hospital discharge (whichever is longer), or to induction of anesthesia to a longer term therapy, which includes a heart transplant or an implant of a surgical RVAD, will be descriptively reported.

   The secondary safety endpoints are major adverse events including death (any cause of death and cardiac death), major bleeding, hemolysis, pulmonary bleeding at hospital discharge or to induction of anesthesia to a longer term therapy. The secondary effectiveness endpoint of improvement in hemodynamic parameters (cardiac index, central venous pressure and LVAD flows) assessed after initiation of Impella RP support. Survival only will be evaluated at 30 days and 180 days post device explant. All secondary endpoints will be descriptively reported.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.