FDA Executive Summary

Prepared for the
April 12, 2016 meeting of the
FDA's Pediatric Advisory Committee

H140001
Impella RP System

Table of Conetents

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience with the use of the Impella RP System. The Impella RP System includes a mini heart pump mounted at the end of a catheter, a console that drives the pump, and an infusion pump that flushes the pump. The heart pump can be implanted in the right side of the heart without open chest surgery to help pump blood in patients who need short-term support. The Impella RP is implanted into the right side of a patient's heart through a small incision in the femoral vein. It helps pump blood from the inferior vena cava, through the heart into the pulmonary artery.

The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include summaries of the premarket clinical study, postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

Note that the firm has also received the marketing approval/clearace for the following devices that are not the subject of this review: Impella 2.5System, Impella 5.0 System, Impella LD System, and Impella CP System.

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 (BSA) $\geq$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.

III. DISCUSSION ON PEDIATRIC USE

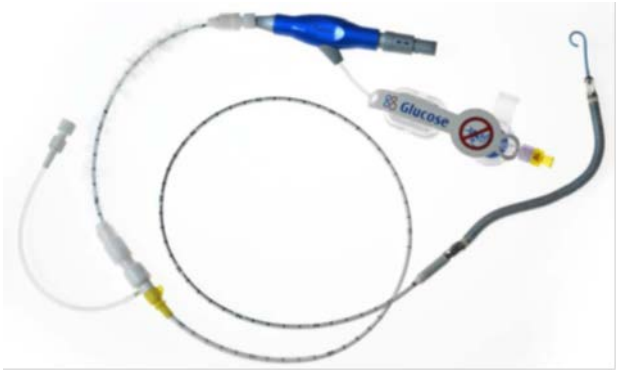
The inclusion criteria, as listed in Section VI, for the pivotal trial included a sub-set of older pediatric patients (from 18 to 21 years old). However, during the trial, there were no patients in this age group enrolled and the youngest patient in the trial was 25 years old. It is expected that a subset of older pediatric patients exists who will be treated with the device, because a sizeable number of pediatric patients receive heart transplants and a significant proportion of these patients are implanted with bridge-to-transplant (BTT) left ventricular assist devices (LVADs) prior to transplant. Based on the computed tomography (CT) fitting study for the Impella RP cannula design completed over a range of BSAs, it is believed that a minimum BSA of ~1.5 m^2 would be compatible for the Impella RP cannula, which corresponds to the average BSA of a 15 year old.

IV. 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, as shown in

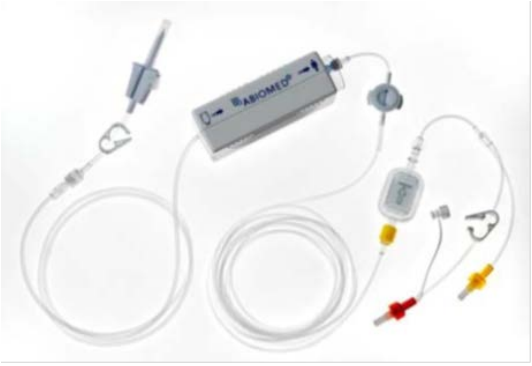
Figure 1:

- 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 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.

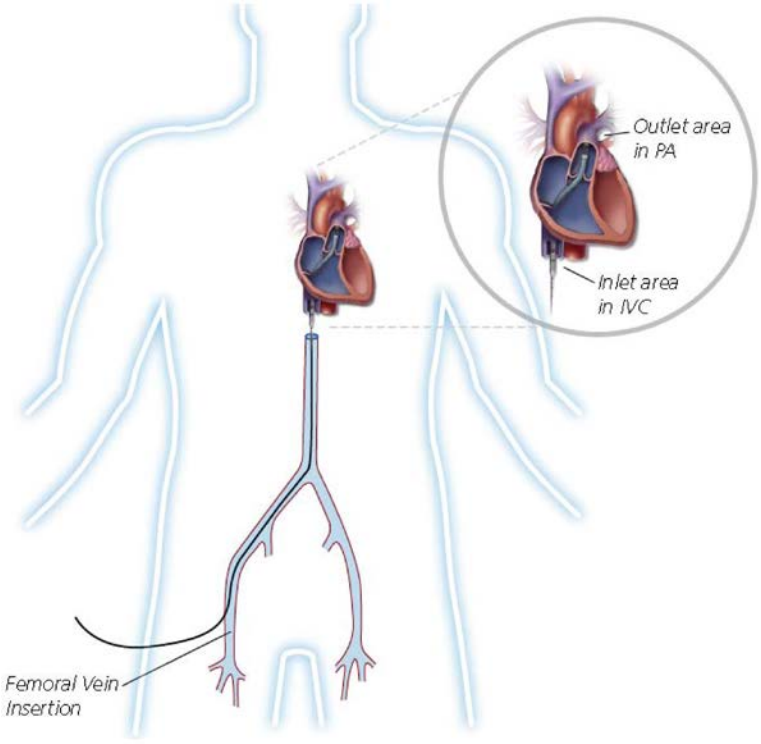


Figure 2: Impella RP Catheter placement during use

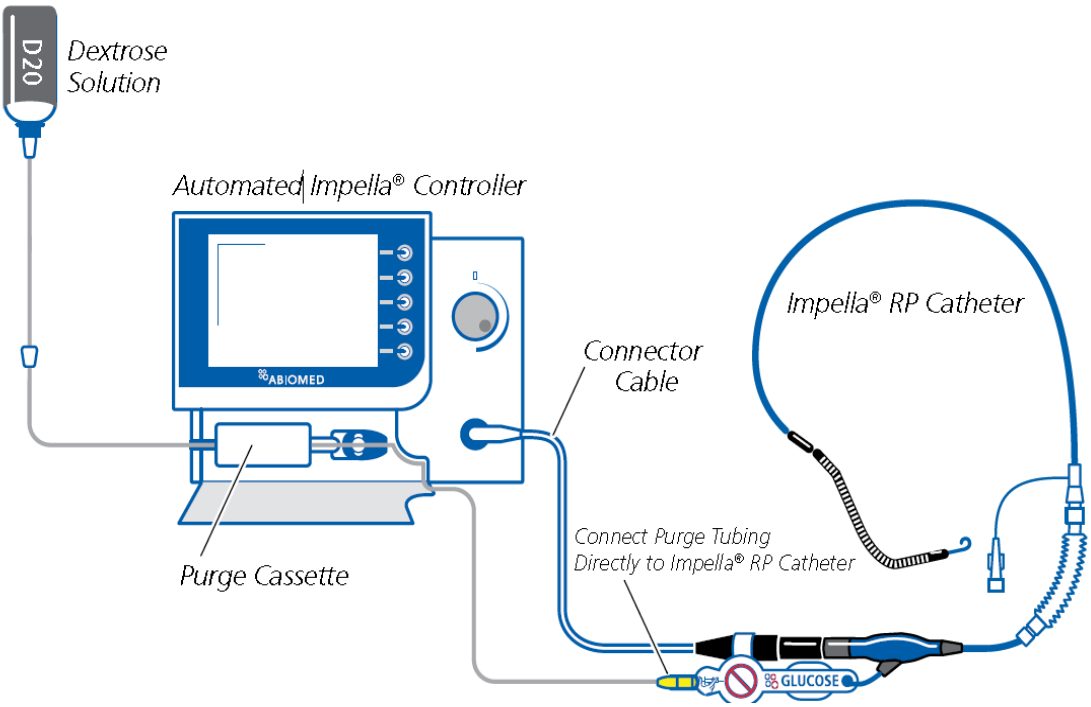


Figure 3: Clinical use set-up for the Impella RP System

V. REGULATORY HISTORY

The device was granted Humanitarian Use Device (HUD) designation on July 13, 2012 by FDA's Office of Orphan Products Development. ABIOMED, Inc. conducted a clinical study (RECOVER RIGHT) of the device in support of their HDE application, and submitted results to FDA in September 2014. The application was approved on January 23, 2015. As a condition of approval, the sponsor was requested to conduct two post-approval studies (PAS), as detailed in Section VII.

VI. PREMARKET DATA

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 probable benefit of the use of the Impella RP device in patients with right ventricular failure (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 right ventricular assist device (RVAD) (as a bridge-to-recovery or bridge-to-transplant).

Secondary probable benefit 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

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. 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
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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

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 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.

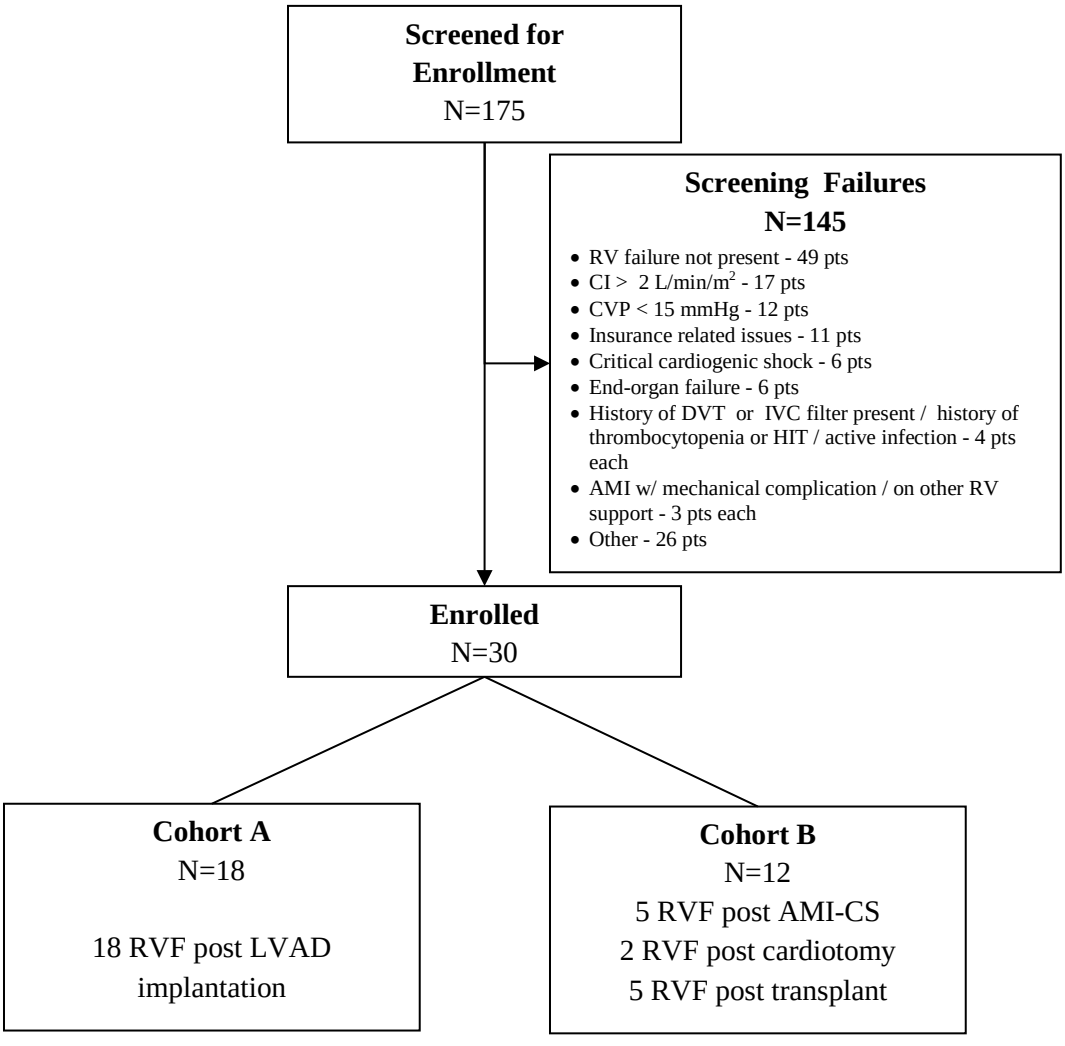


Figure 4: Study flow schematic

C. Study Population Demographics and Baseline Characteristics

The patient baseline characteristics are summarized in Table 1. The mean age was 59±15 years old. Among all patients, 88.5% presented with congestive heart failure (CHF), 60% had history of arrhythmia, 57% had implantable cardioverter defibrillator (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.

Table 1: 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)

Patient Characteristic	All Patients (N=30)	Cohort A (N=18)	Cohort B (N=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 2. 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 2: 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 (g/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 3. Percutaneous placement of the device was attempted through right femoral vein in 96.7% (29 out of 30) cases and through the left femoral vein in 3.3 % (1 out of 30) 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% 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 2.5-4.00 L/min).

Table 3: 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)

Procedural Characteristic	All Patients	Cohort A	Cohort B
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 4. 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 4: 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)

Hemodynamic Characteristics	All Patients Mean±SD (N)	Cohort A Mean±SD (N)	Cohort B Mean±SD (N)
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 5.

Table 5: 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 6.

Table 6: 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)

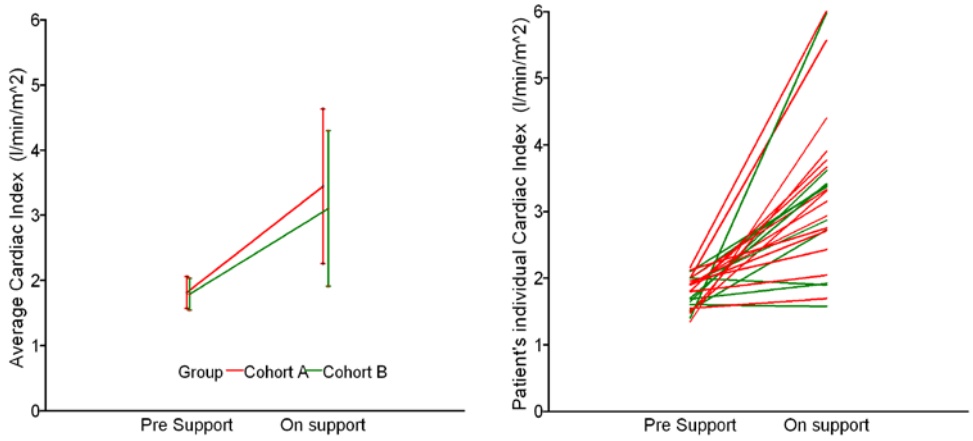
** based on echocardiographic core lab analysis*

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 (93% of the patients lost less than 100 mL of blood for the combined introducer sheath placement and the Impella RP catheter insertion.

G. Secondary Probable Benefit Endpoint Results

<u>CVP and CI improvement post initiation of Impella RP support</u>

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.



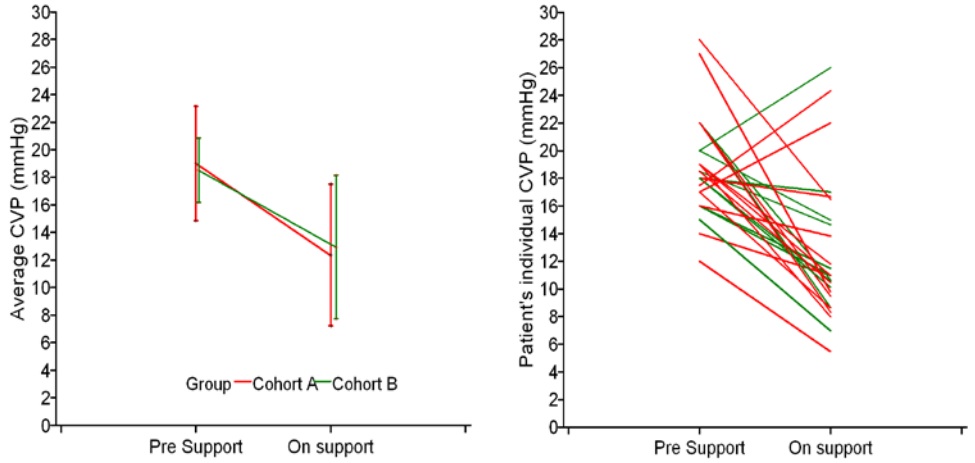


Figure 5: Cardiac index (CI) and central venous pressure (CVP) measured during the study

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.

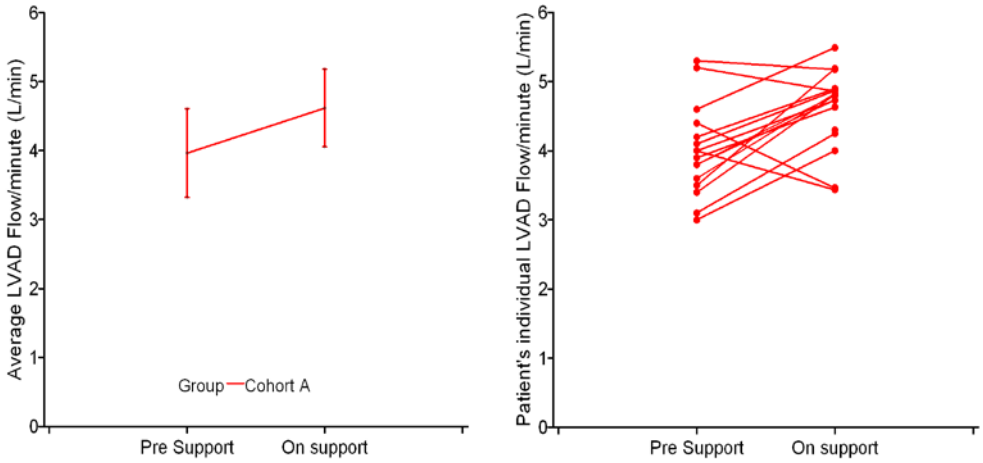


Figure 6: LVAD flow changes from baseline to on-support

In conclusion, the use of 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.

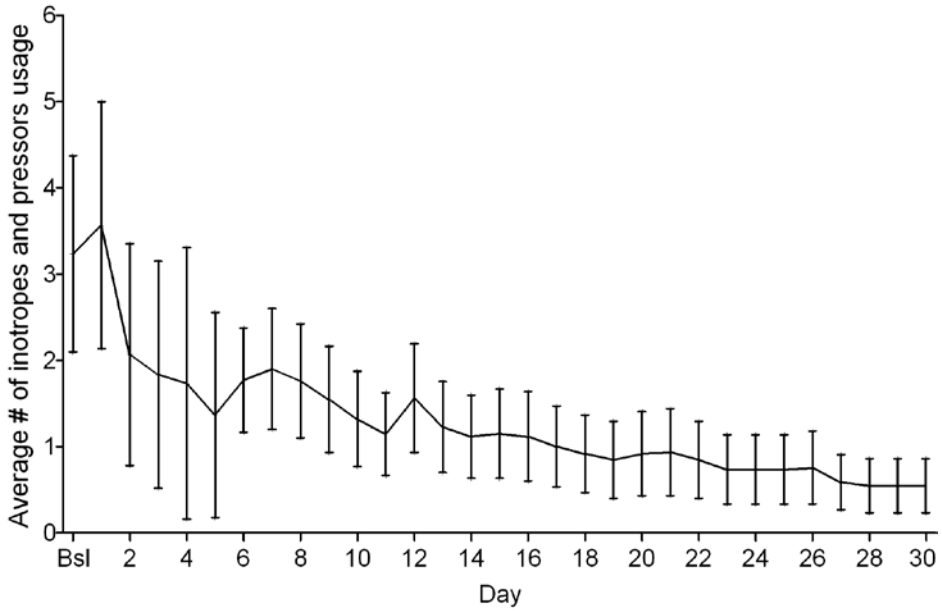


Figure 7: Use of inotropes during and after Impella RP support

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.

Probable Benefit:

- 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.

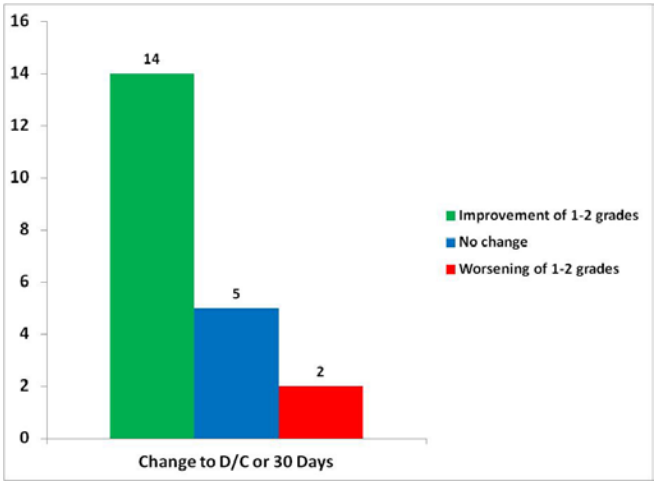


Figure 8: Right ventricular function changes from baseline to 30 days or discharge

- 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 the 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 stopage 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).

VII. ANNUAL DISTRIBUTION NUMBER AND ANNUAL SALES NUMBERS

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and now allows HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN was defined to be the number of individuals affected by the disease or condition per year (i.e., annual incidence) multiplied by the number of devices reasonably necessary to treat an individual. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended the ADN definition to be the number of such devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States, and FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual.

Table 7: Number of devices sold

Calendar Year (Jan - Dec)	Total Sales	Total Implants	Total Pediatric Implants
2015	292	143	0

VIII. POST-APPROVAL STUDIES (PAS')

As a condition of approval, the sponsor is required to conduct two PAS' to monitor the safety and probable benefit of the Impella RP device.

A. Study Designs

PAS1: Impella RP Prospective Study

This is a prospective, multicenter, single arm study enrolling patients with RVF in need of hemodynamic support. Patients will be followed at 30 and 180 days post device explant.

Study population and sample size
The patient population will be similar to the IDE study population. It will comprise of patients with RVF in need of hemodynamic support that meet all inclusion criteria: 1) Patients that develop acute RVF or decompensation after the LVAD implantation, post myocardial infarction, post heart transplant or post open heart surgery, 2) signed informed consent, and 3) BSA $\geq 1.5m^2$ and none of exclusion criteria. Patients with RVF will be supported with the Impella RP until recovery, transplantation or implantation with a long-term device.

Thirty (30) patients will be consecutively enrolled at up to 15 sites in the United States. The sample size follows the same rationale used for the IDE study.

Primary endpoints

- Survival at 30 days post device explant or hospital discharge (whichever is longer), or to induction of anesthesia for a longer term therapy (i.e., heart transplant or RVAD implantation).

Secondary endpoints

Safety

- Survival at 30 days and 180 days post device explant
- The rates of the following serious adverse events (SAEs) measured at hospital discharge or at induction of anesthesia for a longer term therapy (i.e., heart transplant or RVAD implantation):
  - Death (any cause of death and cardiac death)
  - Major bleeding
  - Hemolysis
  - Pulmonary embolism

Effectiveness

- Improvement in the following hemodynamic parameters assessed after initiation of Impella RP support:
  - Cardiac index
  - Central venous pressure
  - LVAD flow

Other adverse events

- Device failures and malfunctions
- Unanticipated adverse device effects (UADEs)

Data collection procedures
Data collected in PAS1 will be based on institutional standards of care for the patient population.

The data collection schedule is presented in Table 8.

Table 8: PAS1 data collection schedules

Clinical Data	Baseline (prior to RP device placement)	Just prior to/during RP placement	Support to device explant	Post explant to discharge	At discharge	30 days post explant	180 days post explant
Demographics	X						
History and Physical Exam	X		X[1]				
Echocardiogram	X		X	X			
Hemodynamics –CI, CO, RAP/CVP, PAP	X		X[2]				
Hematology – WBC/RBC, Platelets, Plasma-free Hgb, Hct/Hgb	X		X[3,5]	X[6]			
Hemostasis – INR or PT or aPTT or ACT	X		X[4]				
Noncardiac Blood Work – Total Bilirubin BUN, Serum Cr and Cr clearance, LDH	X		X[3]	X	X		
Inotropes and pressors and additional RVF medication	X		X	X			
X-Ray Fluoroscopy (for device placement)		X					
Impella RP parameters (performance level and flow)			X				
Adverse Events			X	X			
Completion of					X		

CRF, collection of follow-up contact information							
Phone call to collect survival data						X	X

[1] Physical examination only while on support to device explant
[2] Per institution standard of care (SOC), Q12 hours (±4 hour window) at the minimum
[3] Per institution SOC, once per week at the minimum
[4] ACT/aPTT/PTT- per institution standard of care (SOC), Q12 hours (±4 hour window) at the minimum
[5]Plasma free hemoglobin- daily
[6]Plasma Free Hemoglobin (1 post explant if normal-and daily if abnormal until normalized)

Statistical plan
Patients who develop RVF post LVAD implantation in PAS1 will be compared to Cohort A patients of the IDE study, and patients who develop RVF post myocardial infarction or post-cardiotomy in PAS1 will be compared to Cohort B patients of the IDE study. The combined patients that match Cohort A and Cohort B will be compared to the overall patient population in the IDE study. A direct statistical comparison will not be performed due to the limited sample size and lack of power.

<u>PAS2: Impella RP Pediatric Retrospective Study</u>

This is a single-arm, multicenter, retrospective study of pediatric patients 15 to17 years of age that developed RVF and were supported with the Impella RP device.

Study population and sample size
The study population will comprise of pediatric patients that 1) develop RVF post LVAD implantation, post myocardial infarction, post heart transplant or open heart surgery, 2) age 15-17 years with BSA $\geq 1.5m^2$, and 3) meet none of exclusion criteria.

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

Primary endpoints
- Survival at 30 days post device explant or hospital discharge (whichever is longer), or to induction of anesthesia for a longer term therapy (i.e., heart transplant or RVAD implantation).

Secondary endpoints
Safety
- Survival at 30 days and 180 days post device explant

- The rates of the following serious adverse events (SAEs) measured at hospital discharge or at induction of anesthesia for a longer term therapy (i.e., heart transplant or RVAD implantation):
  - Death (any cause of death and cardiac death)
  - Major bleeding
  - Hemolysis
  - Pulmonary embolism

Effectiveness

- Improvement in the following hemodynamic parameters assessed after initiation of Impella RP support:
  - Cardiac index
  - Central venous pressure
  - LVAD flow

Other adverse events

- Device failures and malfunctions
- UADEs

Enrollment and follow-up

Enrollment will continue until 15 consecutive patients are enrolled or over a period of 5 years, whichever comes first. Patients will be followed at 30 and 180 days post device explant. All events will be followed for the duration of the study until they are resolved or their status is explained.

Data collection procedures

The retrospective data collected will be based on institutional standards of care for this patient population. The data collection schedule is presented in Table 9.

Table 9: PAS2 data collection schedules

Clinical Data	Baseline (prior to device placement)	Just prior to/during placement	Support to device explant	Post explant to discharge	30 days post explant	180 days post explant
Demographics	X					
History and Physical Exam	X		X[1]			
Echocardiogram	X		X	X		
Hemodynamics – CI, CO, RAP/CVP, PAP	X		X[2]			
Hematology – WBC/RBC, Platelets, Plasma-free Hgb, Hct/Hgb	X		X[3]	X		

Hemostasis –INR or PT or aPTT or ACT	X		X[4]			
Noncardiac Blood Work – Total Bilirubin BUN, Serum Cr and Cr clearance, LDH	X		X[3]	X		
Inotropes and pressors and additional RVF medication	X		X	X		
X-Ray Fluoroscopy (for device placement)		X				
Impella RP parameters (performance level and flow)			X			
Adverse Events			X	X		
Phone call to collect survival data					X	X

[1] Physical examination only while on support to device explant
[2] Per institution standard of care (SOC), Q12 hours (±4 hour window) at the minimum
[3] Per institution SOC
[4] ACT/aPTT/PTT- at implant and per institution standard of care (SOC), Q12 hours (±4 hour window) at the minimum

Statistical plan
Patients who develop RVF post LVAD implantation in PAS2 will be compared to Cohort A patients of the IDE study and patients who develop RVF post myocardial infarction or post-cardiotomy in PAS2 will be compared to Cohort B patients of the IDE study. The combined patients that match Cohort A and Cohort B will be compared to the overall patient population in the IDE study. A direct statistical comparison will not be performed due to the limited sample size and lack of power.

B. Status and Results
PAS1: Impella RP prospective Study

Enrollment status
This section presents a summary of the 12-month PAS report submitted by the sponsor. As of the database closing date of January 15, 2016, 8 sites had been activated, two of which had enrolled patients. A total of 77 patients were screened and 13 were enrolled. Sixty–four (64)

patients failed screening due mainly to absence of RVF. No patient had been lost to follow-up. A snapshot of the enrollment status is shown in Table 10.

Table 10: Status of PAS1

	Enrollment Target	Current Enrollment	Percentage (%)
Number of IRB Approvals	15	8	53.3
Number of study sites enrolled	15	8	53.3
Number of subjects enrolled	30	13	43.3
Follow-up rate 30 days post Explant (n=12)*		8	66.7

*includes 3 patients alive at 180 days; data on 1 patient <30 days post implant is pending

Demographic information was available for 12 patients, as summarized below:

- The ages ranged from 46 to 81 years (63 ± 11 year).
- Females constituted 58% (7) of enrolled subjects
- The race distribution was 58% (7) black/African American, 33% (4) white, 8% (1) Asian

Results

Table 11 summarizes the indications for Impella RP implantation in the enrolled patients.

Table 11: Implantation Indications

Indication	n/N	Percentage (%)
RVF after LVAD Implantation	2/13	15
Acute RVF (after open heart surgery or post myocardial infarction)	11/13	85

The outcomes data for the enrolled patients are summarized in Table 12. Eight (8) patients were successfully supported and four (4) patients expired. All four patients who died were weaned; three (3) died in hospital prior to discharge and one (1) died prior to 30 days. One (1) additional patient was weaned and discharged. The outcomes data on this patient was pending (implant date for this patient: 1/6/2016).

Table 12: Summary of PAS1 Treatment Outcomes

	n/N	Percentage (%)
Successfully Supported, Discharged Alive at 180 days	3/12	25
Successfully Supported,	5/12	42

Discharged, Alive at 30 days		
Weaned, Expired in Hospital or prior to 30days	4/12	33

Assessment of Results
The proportion of patients with survival at 30 days post device explant or hospital discharge (whichever is longer) or supported to next therapy is 66.7% (8/12, outcome for 1 patient is pending) of the enrolled patients. This rate is slightly lower than the 73% (22/30) survival rate observed in the IDE study.

The proportion of patients enrolled with an implantable LVAD (Cohort A in the protocol) is 15% (2/13) which is lower than the proportion of Cohort A patients 60% (18/30) in the IDE study.

Considering the current enrollment status of the PAS1, no conclusions can be made at this early stage of the study.

PAS2: Impella RP Pediatric Retrospective Study

Enrollment status
As of the database closing date of January 15, 2016, two (2) pediatric sites had been trained to use the Impella RP during the initial commercial roll-out and had received IRB approval for (HUD) use of the device. However, no pediatric patient had been treated with the device. This is not unexpected, since the pediatric sub-set of the target patient population is expected to be much smaller than the adult sub-set. An updated timeline is shown in Table 13.

Table 13: Timeline for PAS2

HDE Use	**1/1/15**	**1/1/16**	**1/1/17**	**1/1/18**	**1/1/19**	**1/1/20**	**1/1/21**
Site Use							
PAS HDE Site 1		P_e	P_e	P_e			
PAS HDE Site 2		P_e	P_e	P_e	P_e		
PAS HDE Site 3		P_e	P_e	P_e	P_e		
PAS HDE Site 4		P_e	P_e	P_e	P_e	FPF	
PAS HDE Site 5		P_e	P_e	P_e	P_e		
PAS Reports	PR1	PR2 PR3	PR4	PR5	PR6	PR7	FR*

P_e: Patient Enrolled; FPF- Final Patient Follow-up (6 months); PR- Periodic Report; FR- Final Report (*to be submitted 3 months after FPF)

Assessment
Per the timeline, 5 complete years are required to enroll a total of 15 patients, which is consistent with the approved protocol.

IX. POSTMARKET LITERATURE REVIEW

A search of the literature was conducted for articles published on Impella from January 23, 2015 (date of Impella RP approval) to November 30, 2015. The search was conducted using pre-specified criteria and the following search terms “Right intracardiac microaxial pump” OR “Right ventricular support rotary blood pump” OR “Right intra-cardiac short term assist” OR “RVAD” OR “Impella RP” OR “Impella right percutaneous” OR “Mechanical support

AND Impella" OR Percutaneous Right Ventricular Impella" OR "Percutaneous Right Ventricular Assist Device." The search term combinations yielded 44 articles. There were 3 articles on Impella 2.5/5.0 or LVAD (different from the subject device) and one (1) article based on the data from the Impella RP pivotal study that was submitted to FDA for device approval[1]. There were no other published clinical studies on the Impella RP System.

X. MEDICAL DEVICE REPORTS (MDRS)

A. Overview of MDR Database

Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations;
  - off-label use; and
  - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect

relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

B. MDRs Associated with Impella RP System

The Agency received two MDRs related to the Abiomed Impella RP System which were entered into FDA's MDR database between the approval date of January 23, 2015 and November 30, 2015. The MDRs were reviewed for factors such as reported device and patient problems, event type, report source, patient age, patient gender, reporting country and the time to event occurrence (TTEO). The TTEO is based on the implant duration specified in the event text of the MDR or calculated as the time period between the date of implant and date of event.

No MDRs involving pediatric patients were received in this time period. Patient age and gender were provided in both MDRs. The two patients were adult males who were both 54 years of age.

There was one MDR reported by the manufacturer and one MDR reported from a user facility (UF). These MDRs were related to two separate events. One event was a death event and one was a serious injury event.

The reporting country was listed as the United States for both MDRs.

Type of Events

The two MDRs were individually reviewed and are detailed to include specific event, patient information, TTEO and required intervention, as provided in the reports.

- Death Event (n=1)
  - There was one death event involving a 54 year old male patient who had a left ventricular assist device (LVAD) implanted two weeks prior to placement of Impella RP. During introducer sheath placement in preparation for Impella insertion, there was bleeding from the OSCOR sheath valve related to off-center insertion of the Swan-Ganz catheter through the sheath. The bleeding continued throughout the procedure requiring a blood transfusion of 4 units of blood. The patient was supported for 16 days and continued to decompensate due to underlying pulmonary hypertension, vasodilatation and sepsis. The Impella was removed, the family withdrew care, and the patient expired the next day.

- Injury Event (n=1)
  - There was one injury event involving a 54 year old male patient who was supported on an LVAD. Seven days after placement of the Impella RP, the patient started having high purge pressures and corresponding decrease in flow. The patient experienced an increase in arrhythmias. Due to the rise in purge pressure, the patient weaning procedure was initiated. LVAD flows remained stable and the Impella was explanted. Manufacturer analysis of the returned device identified a thrombus on the pump inflow window and into the purge gap causing purge pressures to rise. According to the manufacturer's investigation, the patient's anticoagulation therapy was interrupted during use of the Impella which contributed to the thrombus formation and rise in purge pressures.

Conclusions
There are no pediatric patients reported in the MDRs.

The risks and complications reported in the MDRs have been reported in the IDE study, have been identified in the instructions for use (IFU) and reflect known complications of this type of device.

XI. SUMMARY

The FDA did not identify any new safety signals during this review of the Impella RP System HDE annual report, the MDRs received, and the peer-reviewed literature published since the initial approval. As such, the FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue our routine monitoring of the safety and distribution information for this device.

XII. REFERENCES

1. Anderson MB, Goldstein J, Milano C, Morris LD, Kormos RL, Bhama J, Kapur NK, Bansal A, Garcia J, Baker JN, Silvestry S, Holman WL, Douglas PS, O'Neill W. Benefits of a novel percutaneous ventricular assist device for right heart failure: The prospective RECOVER RIGHT study of the Impella RP device. J Heart Lung Transplant 2015;34:1549–1560.