

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

### I. GENERAL INFORMATION

Device Generic Name: Temporary Ventricular Support Device

Device Trade Name: Impella Ventricular Support Systems

Device Product Code: OZD

Applicant Name and Address: Abiomed, Inc.  
22 Cherry Hill Drive  
Danvers, MA 01923

Date of Panel Recommendation: None

Pre-market Approval (PMA) Number: P140003/S004

Date of Notice of Approval to Applicant: April 7, 2016

The original PMA for the Impella 2.5 System (PMA P140003) was approved on March 23, 2015. The approved indication for use for the Impella 2.5 System is:

*The Impella 2.5 System is a temporary (< 6 hours) ventricular support device indicated for use during high risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high risk PCI is the appropriate therapeutic option. Use of the Impella 2.5 in these patients may prevent hemodynamic instability which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.*

Additional information about the Impella 2.5 System is available in its Summary of Safety and Effectiveness Data (SSED), which can be found on the FDA CDRH web-site.

The purpose of this supplement (P140003/S004) is to expand the indication for use to include the treatment of ongoing cardiogenic shock that occurs immediately following acute myocardial infarction and to include additional Impella Catheters for this indication

## **II. INDICATIONS FOR USE**

The Impella 2.5, Impella CP, Impella 5.0, and Impella LD catheters, in conjunction with the Automated Impella Controller, are temporary ventricular support devices intended for short term use (< 4 days for the Impella 2.5 and Impella CP, and ≤ 6 days for Impella 5.0 and LD) and indicated for the treatment of ongoing cardiogenic shock that occurs immediately (< 48 hours) following acute myocardial infarction or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures.\* The intent of the Impella system therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function.

*\*optimal medical management and conventional measures include volume loading, use of pressors and inotropes support with or without IABP.*

## **III. CONTRAINDICATIONS**

- Mural thrombus in the left ventricle
- Presence of a mechanical aortic valve or heart constrictive device
- Aortic valve stenosis/calcification (equivalent to an orifice area of 0.6 cm<sup>2</sup> or less)
- Moderate to severe aortic insufficiency (echocardiographic assessment graded as ≥ +2)
- Severe peripheral arterial disease precluding placement of the Impella Catheters
- Significant right heart failure
- Combined cardiorespiratory failure
- Presence of an atrial or ventricular septal defect (including post-infarct VSD)

- Left ventricular rupture
- Cardiac tamponade

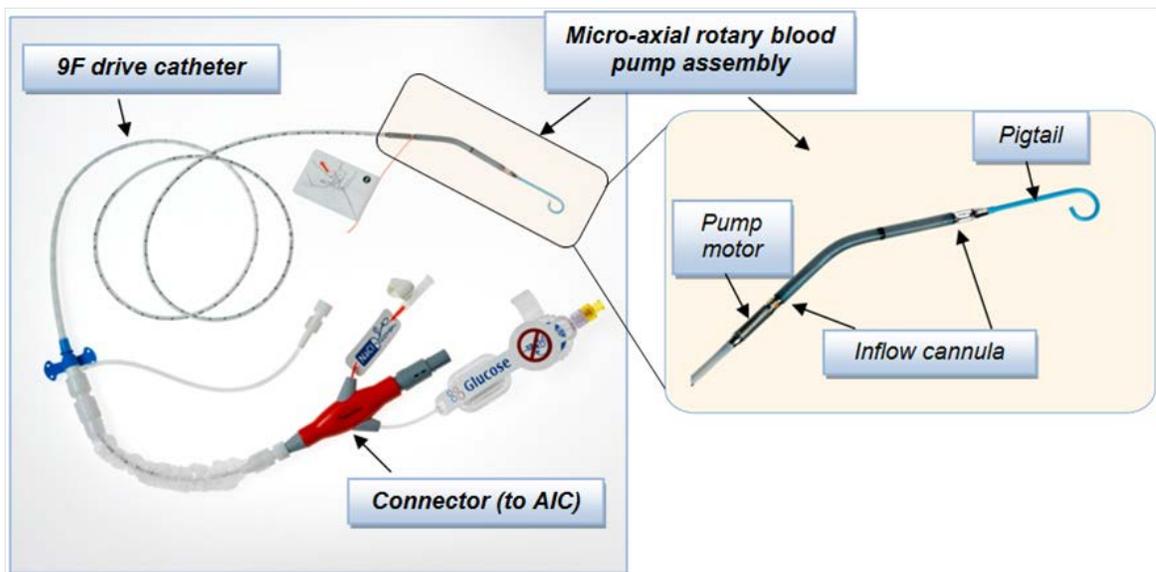
#### IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the approved labeling for the Impella Ventricular Support Systems.

#### V. **DEVICE DESCRIPTION**

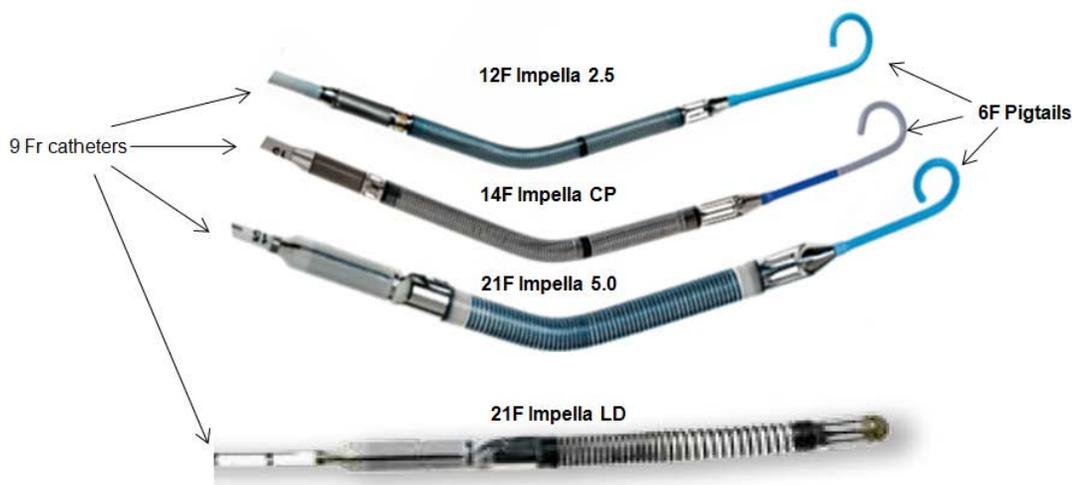
To accommodate a range of cardiac flow requirements, different sized Impella Support Catheters are available. Figure 1 shows general overall design for the Impella Catheters. All of the Impella Catheters consist of a micro-axial rotary blood pump mounted on a 9F drive catheter, which is connected to an external controller, the Automated Impella Controller (AIC).

Figure 1: Impella Ventricular Support Catheter Design



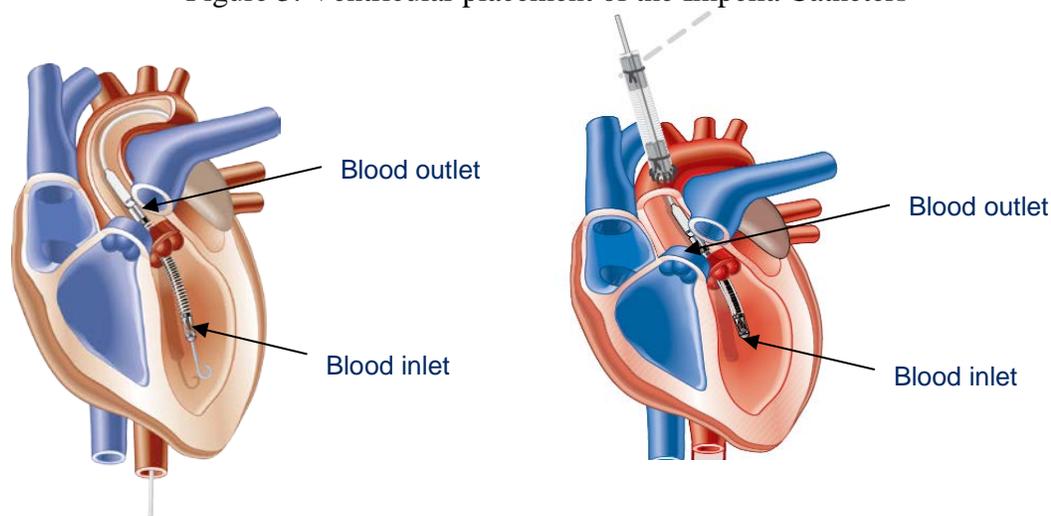
There are four different Impella Catheters, as shown in Figure 2. The peripherally placed catheters are the Impella 2.5, the Impella CP and the Impella 5.0, which have blood pump diameters of 12F, 14F and 21F, respectively. In addition, a fourth 21F surgically placed Impella Catheter, the Impella LD is available.

Figure 2: The Impella Ventricular Support Catheters



The Impella Catheters shown above are all placed with the cannula inflow located in the left ventricle and the outflow located in the ascending aorta, as shown in Figure 3. Blood is drawn through the cannula situated in the left ventricle and expelled into the aorta. As shown in Figures 2 and 3, the three peripherally placed pumps (the Impella 2.5, Impella CP and Impella 5.0) have 6F pigtails attached to their tips, to enable device placement over the wire and positioning in the correct anatomical position. When placing an Impella Catheter peripherally (via a guidewire), the device is loaded over the wire through the pigtail. The Impella 5.0, while placed peripherally, requires a graft and a surgical cut-down and can access the circulation through either the femoral or axillary artery. Alternatively, the Impella LD is surgically placed directly through the aorta into the heart (see in Figure 3).

Figure 3: Ventricular placement of the Impella Catheters

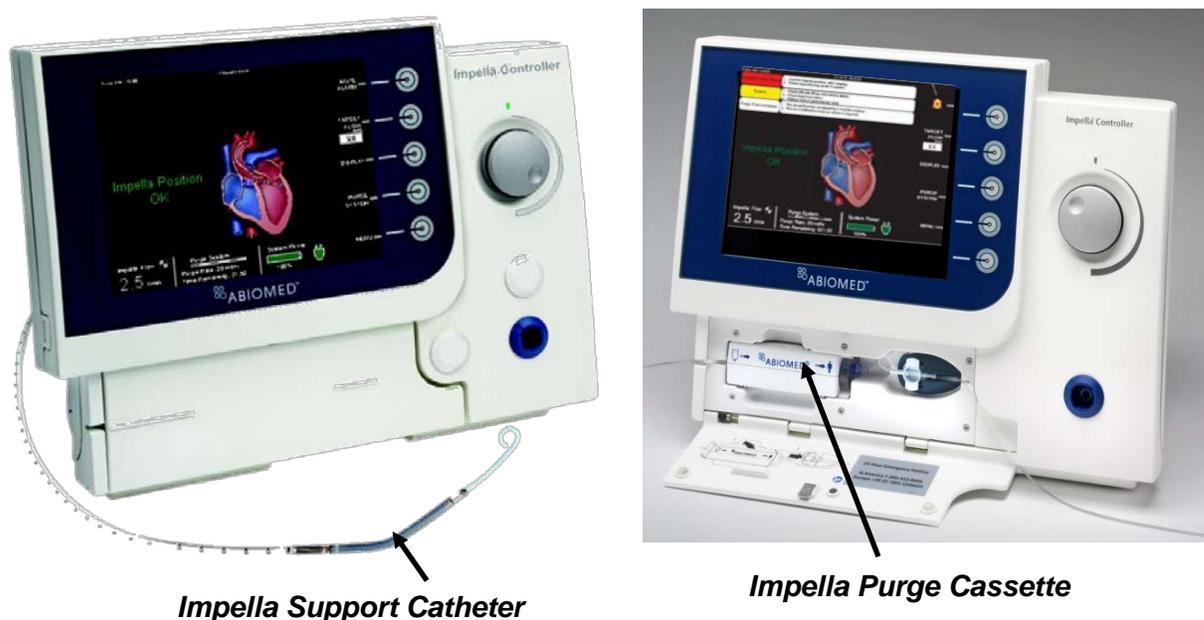


**Percutaneous Catheter Placement  
(Impella 2.5, Impella CP, Impella 5.0)**

**Surgical Catheter Placement  
(Impella LD)**

The Impella Catheters are all operated by the same external drive console, the Automated Impella Controller (AIC), shown in Figure 4. The AIC generates signals required to power the drive motor of the Impella Catheters and provides a user interface. The AIC also incorporates the disposable Impella Purge Cassette system, which provides a fluid pressure barrier to prevent blood from entering the Impella Catheters' drive motor. A dextrose (5-40% with 50 Units/ml of heparin added) solution is used as a purge fluid. The AIC is portable and has been qualified for use for patient transport by trained healthcare professionals within healthcare facilities and during medical transport between hospitals (i.e., ambulance, helicopter or fixed-wing aircraft).

Figure 4: The AIC with an Impella Catheter and its Impella Purge Cassette



Additional sterile, disposable implant accessories are provided with the Impella Catheters to assist in their percutaneous insertion. For the Impella 2.5, these components are a 13F peel-away introducer kit (manufactured by Merit Medical) and an 0.018” placement guidewire (manufactured by Lake Region Medical). The Impella CP accessories are a 14F peel-away introducer kit (manufactured by Oscor Medical) and the identical placement guidewire packaged with the Impella 2.5. The Impella 5.0 is packaged with a 23F peel-away introducer kit (manufactured by Oscor Medical), an 0.018” guidewire (manufactured by Lake Region Medical), and a surgical clamp to assist in hemostasis.

A reusable cart for the AIC is also provided for ease of patient transport within the hospital.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

The alternative therapies used to treat left ventricular function (LVF) in this setting are inotropic support, intra-aortic balloon pump (IABP) counterpulsation therapy, or surgical left ventricular devices.

## **VII. MARKETING HISTORY**

The Impella pumps have received CE Mark in the European Union (EU) as well as approval in Canada for a similar intended use as is being approved in this supplement. Neither the AIC nor any of the Impella pumps have been withdrawn from marketing for any reason related to its safety or effectiveness.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The following adverse events may be associated with use of the Impella Ventricular Support Systems:

- Acute renal dysfunction
- Aortic insufficiency
- Aortic valve injury
- Atrial fibrillation
- Bleeding
- Cardiogenic shock
- Cardiac tamponade
- Cardiopulmonary resuscitation
- Cerebral vascular accident/Stroke
- Death
- Device malfunction
- Failure to achieve angiographic success
- Hemolysis
- Hepatic failure
- Insertion site infection
- Limb ischemia
- Myocardial infarction
- Need for cardiac, thoracic or abdominal operation
- Perforation
- Renal failure
- Repeat revascularization
- Respiratory dysfunction
- Sepsis
- Severe hypotension
- Thrombocytopenia
- Thrombotic vascular (non-CNS) complication
- Transient ischemic attack
- Vascular injury
- Ventricular arrhythmia, fibrillation or tachycardia

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

## **IX. SUMMARY OF PRECLINICAL STUDIES**

Preclinical testing was conducted on the Impella 2.5 Catheter, the AIC, and the Impella Purge Cassette in support of P140003 and summaries can be found in the original SSED, here: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf14/P140003b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003b.pdf). The testing summarized below was reviewed to support the increased duration of use for the new AMICS indication (the original indication was for <6 hours, while the AMICS indication is for 4-6 days) and to support the addition of the additional Impella Catheters (Impella CP, Impella 5.0, and Impella LD).

### **A. Laboratory Testing**

In-vitro studies were performed for the Impella Ventricular Support Systems, including the disposable components, specifically the Impella Support Catheters. The results of the in-vitro studies were combined with the animal study results and the clinical results in the overall review of safety and effectiveness the Impella Ventricular Support Systems.

#### **Biocompatibility Studies**

Toxicology and biocompatibility tests for the Impella Catheters were conducted in accordance with Good Laboratory Practices (21 CFR §58) and ISO 10993-1: 2003 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. All acceptance criteria were met.

#### **Structural Integrity Testing**

Structural tests of each Impella Catheter's components were conducted. Summaries of the test results for the Impella Catheters are provided in Table 2.

Table 2: Summary of Structural Integrity Testing on Impella Catheters and Accessories

<b>Test</b>	<b>Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Bend	This test verified that the Impella catheters can survive the bending stresses expected during clinical use.	All catheters tested must remain intact/functional after their bend tests (for their intended durations of use).	Passed
Tensile	This test verified that the Impella catheters joints strengths are compatible with the forces expected during clinical use.	Under tensile load, all joint strengths must exceed their pre-set tensile limits.	Passed
Temperature	This test verified that the temperature of the Impella catheters' blood contacting surfaces were acceptable for clinical use.	The surface temperatures must remain below a maximum allowable temperature.	Passed
Fluid Tightness (Introducer System)	This test verified that the Impella catheters' introducer systems were acceptable with minimal blood loss during clinical use.	Each introducer system must not leak more than its pre-set amount during simulated use.	Passed

Electrical Compatibility, Immunity Standards & Safety Testing

The Impella Ventricular Support Systems (all of the Impella Catheters, the AIC and the Impella Purge Cassette) were tested for Electromagnetic Compatibility (EMC), Electromagnetic Immunity (EMI), and Electrical Safety against the relevant national and international standards. Testing verified compliance to recognized FDA Standards, including to IEC 60601-1, 2<sup>nd</sup> and 3<sup>rd</sup> editions. Where applicable, testing was also performed in accordance with IEC 60601-1-2 *Issued: 2007* (3<sup>rd</sup> edition). All of the EMC, EMI and Electrical Safety tests passed.

## Performance Testing

Performance tests for the Impella Catheters were conducted. Summaries of the test results are provided in Table 3.

Table 3: Summary of Performance Testing on Impella Catheters and Accessories

<b>Test</b>	<b>Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Flow Characterization	This test verified that the Impella catheters provided their specified flow, and that the flow was accurately reported (on the AIC) for the expected range of clinical use conditions.	The Impella catheters' flow must be within a pre-set range, and be reported correctly ( $\pm 0.3$ LPM versus an external flow meter) over the pre-set range tested.	Passed
Simulated Placement & Cannula Kink	This test verified that the Impella catheters can be easily placed using their introducer systems and will not kink during use.	Simulated delivery must meet a pre-defined ease of use criteria, and each catheters' cannulae must not kink (at a pre-set diameter).	Passed
Computer Fluid Dynamics (CFD)	This test evaluated the flow fields in the Impella pumps to quantify pressure and fluid stress levels in the pumps.	The pressures & fluid stress levels must remain within pre-set limits (compatible with red blood cell survival).	Passed
Hemolysis	This test (run in accordance with ASTM F1841-97(2005)) verified that the Impella catheters would not cause excessive blood hemolysis when run at their maximum flow setting.	Each catheters' hemolysis profiles must be equivalent to other approved devices, and must meet their design requirement (must be less than a pre-set Modified Index of Hemolysis (MIH)).	Passed

### Reliability Testing

Reliability tests of the Impella catheters were conducted. The purpose of the testing was to demonstrate that each Impella catheter has acceptable reliability for its intended duration of use. Multiple pumps were tested in a customized test loop, which was designed to mimic the clinical use conditions (e.g., the temperature, flow, and pressure). The test duration was to twice the intended duration of use. The pre-set pass/fail criteria were related to the reliability and confidence levels appropriate for temporary life support devices. All of the Impella catheters were tested, and all of tests were completed successfully (i.e., the acceptance criteria were met). The results of the tests support the approved intended durations of use (See Section II above).

### Hazard Analysis

Potential hazards associated with the use of the Impella Ventricular Support Systems, in both normal operation and potential abnormal conditions, were identified and analyzed for their short-term and long-term effects. This information was used in Abiomed's internal hazard analysis process. Based on this analysis, measures were taken to minimize the occurrence of the hazards and the remaining risks were deemed to be acceptable.

## **B. Animal Studies**

Extended animal studies were completed to evaluate each Impella catheter. The purpose of the testing was to demonstrate the safe use of the Impella catheter for extended implant durations, which were up to 5 days, 12 days, and 10 days for the Impella 2.5, Impella CP, and Impella 5.0/LD, respectively. Each study had pre-set acceptance criteria related to safe device use, which included a hemolysis endpoint, evaluation of potential heart device interactions, and animal survivability/adverse events. In addition, the study endpoints included an assessment of overall in vivo device performance. Overall, the animal tests were successfully completed, and the endpoints were met for each study. The animal studies validated that each Impella catheter could be used safely in animals for its intended duration of use without causing adverse reactions or unexpected product performance failures or malfunctions.

### **C. Sterilization**

The Impella Catheters are all sterilized using 100% ethylene oxide (EO). The sterilization process was 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 11135:1994, ANSI/AAMI/ISO 14937:2000 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 10993-7:1995.

### **D. Shelf Life**

Packaging and product integrity studies were conducted to ensure that the shelf life for each package and product is maintained for a minimum of two (2) years for all of the Impella Catheters and Impella Purge Cassette. A suite of tests were completed to verify that two (2) years of aging does not affect key aspects of the device safety or performance. Testing was also completed to demonstrate packaging integrity for 2 years of shelf life. All of the shelf tests passed.

## **X. SUMMARY OF PRIMARY CLINICAL STUDIES**

### **ISAR-SHOCK Clinical Study**

The ISAR-SHOCK trial was designed as a prospective, two-center, randomized, open-label study designed to test whether the Impella 2.5 provides superior hemodynamic improvement as compared to the standard procedure utilizing IABP for patients with acute myocardial infarction with cardiogenic shock (AMICS).

#### **A. Study Design**

The trial was designed to assess the hemodynamic robustness of the Impella 2.5 against IABP (primary endpoint), as measured by the improvement of cardiac support after device support initiation. Safety data (survival and adverse events) were also studied (secondary endpoints). Details of the study design are below.

##### **1. Clinical Inclusion/Exclusion Criteria**

Eligible patients were those who presented with cardiogenic shock within 48 hours of an acute myocardial infarction or suspicion of an acute coronary syndrome. The inclusion and exclusion criteria are below.

*Inclusion Criteria:*

- Systolic Blood Pressure (SBP) < 90 mmHg during angina pectoris and heart rate > 90/min OR use of catecholamines to maintain SBP > 90 mmHg during angina pectoris; AND
- Signs of end-organ hypoperfusion OR Signs of left ventricular failure (Killip class 3 or 4).
- Left Ventricular Ejection Fraction (LVEF) < 30% and Left Ventricular End-Diastolic Pressure (LVEDP) > 20 mmHg OR
- Cardiac Index (CI) < 2.2 l/min/m<sup>2</sup> and Pulmonary Capillary Wedge Pressure (PCWP) > 15 mmHg.

*Exclusion Criteria (Clinical only)*

- Age less than 18 years old
- Resuscitation for more than 30 minutes
- Obstructive, hypertrophic cardiomyopathy
- Marginal thrombus in the left ventricle
- Subjects with implanted IABP at the point in time of randomization
- Mechanical mitral and/or aortic valve, and/or severe valve stenosis
- Mechanical cause of cardiogenic shock
- Right ventricular failure
- Sepsis
- Brain damage or suspicion of brain damage
- Surgically uncontrollable bleeding
- Massive pulmonary embolism
- Known coagulopathy or allergy to heparin
- Aortic insufficiency
- Participation in another clinical study
- Pregnancy

## 2. Follow-up Schedule

Patients were followed up to 6 months. Procedural, hemodynamic, blood data and concomitant medications including catecholamines requirement were collected at baseline and at different times as prescribed by the protocol. Adverse events were recorded throughout the duration of the study.

## 3. Clinical Endpoints

### *Primary Endpoint-*

- Hemodynamic improvement within the first 60 minutes after implantation, as measured by an improvement in cardiac index (CI) immediately following implantation of the study support device.

### *Secondary Endpoints-*

- Hemodynamic change during the course of treatment, which is defined as the change in measured values from the baseline (pre-implantation) after 24 and 48 hours using a generally recognized catecholamine dosage.
- Change in the catecholamine dosage for adrenalin or dobutamine from baseline compared to 6, 24, 48 and 96 hours after implantation.
- Survival for 30 days.
- Rates of all adverse events up to 30 days post-implantation.
- Lactate release (defined as a change in the lactate value from baseline compared to 6, 24, 48 and 96 hours after implantation).

## **B. Accountability of PMA Cohort**

Twenty-seven (27) subjects were enrolled in ISAR-SHOCK at 2 centers in Germany between September 15, 2004 and February 17, 2007. Fourteen (14) patients were randomized to the Impella arm and 13 patients to the IABP arm. One (1) patient in the Impella arm (A-03-a) withdrew following consent, but prior to initiation on support. No data was captured for this patient. In addition, one (1) patient in the Impella arm (B-07-a) expired after randomization but prior to device placement.

### C. Study Population Demographics and Baseline Characteristics

Study population demographics, characteristics and hemodynamics are provided below.

Table 4: Baseline demographics and characteristics

<b>Parameter</b>	<b>All Subjects</b>	<b>IABP</b>	<b>Impella 2.5</b>	<b>p-value</b>
Number of subjects	26	13	13	
Age in years (mean ± SD)	65 ± 13	67 ± 15	63 ± 10	0.390
Male %, (number)	73% (19)	85% (11)	62% (8)	0.378
LVEF % (mean ± SD)	27 ± 11	28 ± 12	26 ± 11	0.619
Number of catecholamines at baseline (mean ± SD)	1.2 ± 0.7	1.0 ± 0.4	1.3 ± 0.9	0.253
Diabetes %, (number)	27% (7)	8% (1)	46% (6)	0.030
Smoking %, (number)	42% (11)	46% (6)	38% (5)	1.000
Hypercholesterolemia %, (number)	38% (10)	38% (5)	38% (5)	1.000
Arterial Hypertension %, (number)	38% (10)	54% (7)	23% (3)	0.370
Anterior myocardial infarction (number) %	50% (13)	54% (7)	46% (6)	1.000
Time from AMI to support device implant in hours (mean ± SD)	9.9 ± 6.4	9.4 ± 6.6	10.4 ± 6.5	0.696

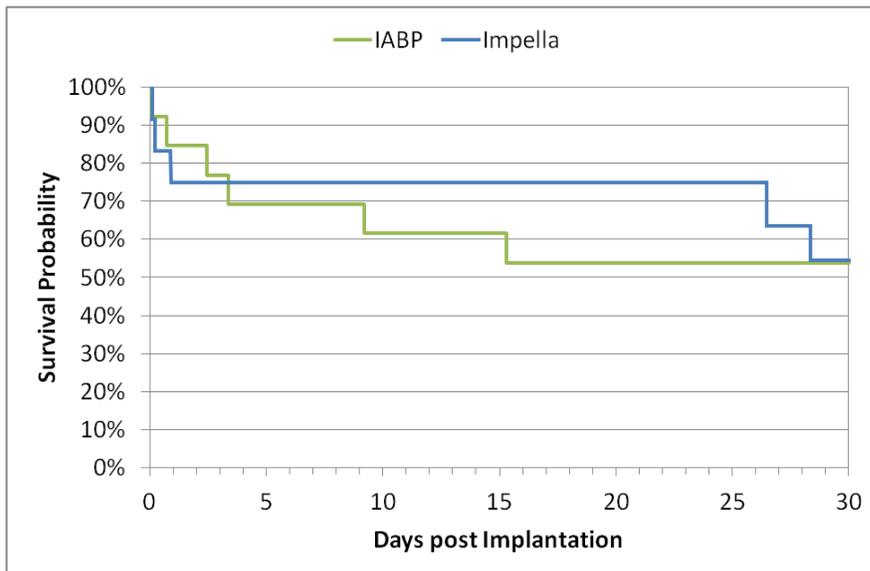
Table 5: Baseline hemodynamics

<b>Parameter</b>	<b>All (mean ± SD) (n=25)</b>	<b>IABP (mean ± SD) (n=13)</b>	<b>Impella 2.5 (mean ± SD) (n=12)</b>	<b>p- value</b>
Cardiac Index [l/min/m <sup>2</sup> ]	1.8 ± 0.6	1.8 ± 0.8	1.7 ± 0.5	0.820
Heart rate [bpm]	96.8 ± 24.7	97.9 ± 24.7	95.5 ± 25.8	0.820
Systolic art. pressure [mmHg]	104.0 ± 21.4	98.6 ± 21.5	109.8 ± 20.6	0.196
Diastolic art. pressure [mmHg]	60.8 ± 14.3	56.5 ± 12.4	65.5 ± 15.2	0.117
Mean arterial pressure [mmHg]	74.9 ± 15.9	71.0 ± 15.6	79.2 ± 15.8	0.206
Systemic vasc. resistance [dyn sec <sup>-5</sup> ]	1605 ± 620	1569 ± 775	1647 ± 399	0.766
Pulmonary capillary wedge pressure [mmHg]	22.1 ± 7.2	21.5 ± 6.7	22.8 ± 8.0	0.685
Central venous pressure [mmHg]	12.4 ± 6.3	12.3 ± 5.6	12.6 ± 7.3	0.916
Lactate [mmol/l]	6.5 ± 4.3	6.6 ± 4.0	6.5 ± 4.7	0.947

#### **D. Safety and Effectiveness Results**

The safety endpoint, 30-day survival, which was the secondary endpoint in the trial, is provided in Figure 5. There was an initial trend for better survival for Impella 2.5 while on device support but late death events occurred with no difference at 30 days. The study was not powered for survival differences to be established between devices considering the limited sample size; therefore, no definitive statement with respect to survival benefit can be made.

Figure 5: Kaplan-Meier survival curves survival (to 30 days) for the ISAR-SHOCK trial



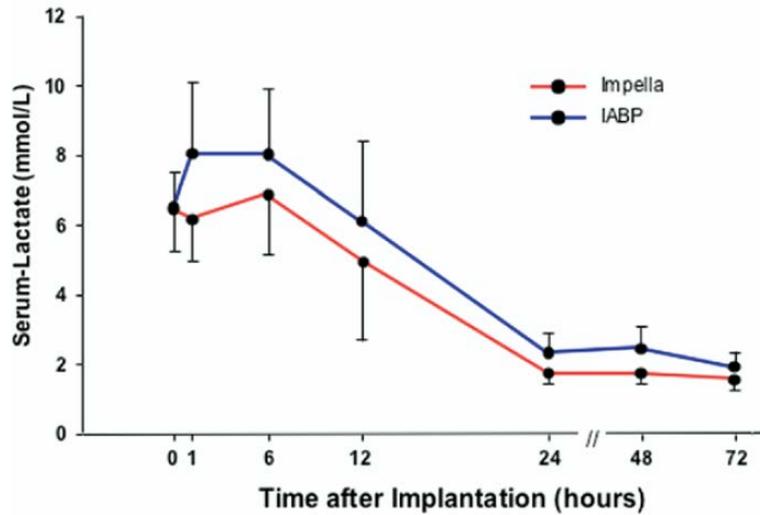
In addition, adverse events (AEs) were monitored for the trial for 30 days post-implant as secondary endpoint. There were no serious adverse events (SAEs) reported. There were four (4) non-serious AEs reported, as shown in Table 6.

Table 6- Non-serious adverse events reported through 30-day time point

Cohort	Adverse Event(s)	Outcome
Impella	Bleeding at insertion site	Manual compression needed (for 20 minutes)
	Hemolysis (two consecutive blood samples)	Resolved in 1 day
	Hematoma at insertion site	Resolved in 1 week
IABP	Ventricular tachycardia	Resolved in 1 day

A third safety endpoint, the lactate levels following support, was monitored. This data is given in Figure 6. The results were similar for both study cohorts.

Figure 6: Lactate levels seen post-implant during the trial



The effectiveness endpoint, which was the primary endpoint of the study, was the change of cardiac index from baseline after device support. The ISAR-SHOCK study showed a significant improvement of cardiac index in the Impella 2.5 arm compared to the IABP arm post-device insertion, as shown in Figure 7. In addition, after 24 hours of support, fewer patients supported with the Impella 2.5 required inotropes compared to patients supported with an IABP, as shown in Figure 8.

Figure 7: Increase in cardiac index from baseline, Impella vs. IABP 30 minutes post-support, in patients treated for cardiogenic shock after an AMI (ISAR-SHOCK)

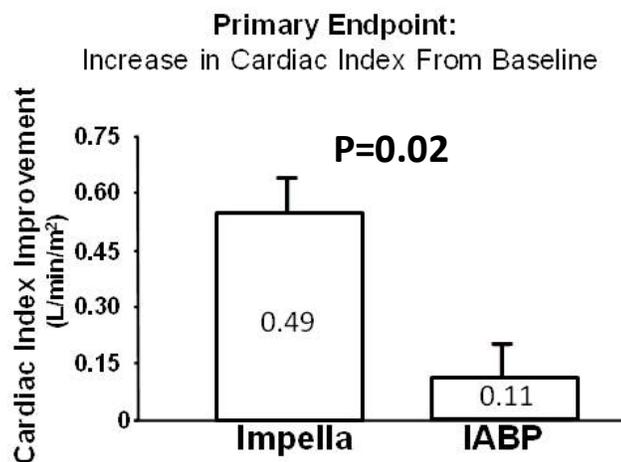
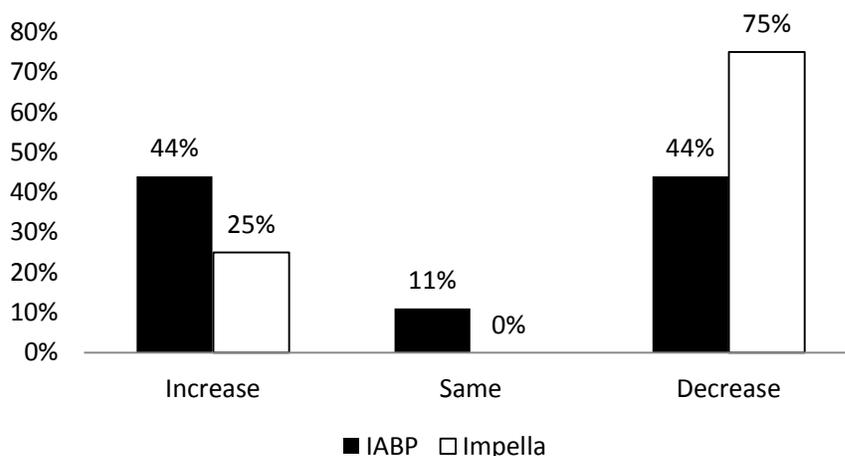


Figure 8: Change in inotropic dosage at 24 hours, Impella vs. IABP in patients treated for cardiogenic shock after an AMI (ISAR-SHOCK)



**E. Device Failures and Replacements**

There were no device failures or replacements reported during the study.

**F. 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. This clinical study included 2 investigators. Neither 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.

**XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

Supplemental data from the Impella registry was provided to demonstrate real world use for the patient population. Several analyses of the Impella Registry data were provided to support the safety and effectiveness of use of the Impella devices. An analysis of the Impella Registry was also provided to differentiate the outcomes for different treatment groups. In addition, the sponsor also provided a benchmark comparison of the Impella Registry data to a comparable registry dataset for its surgical VAD, the AB5000

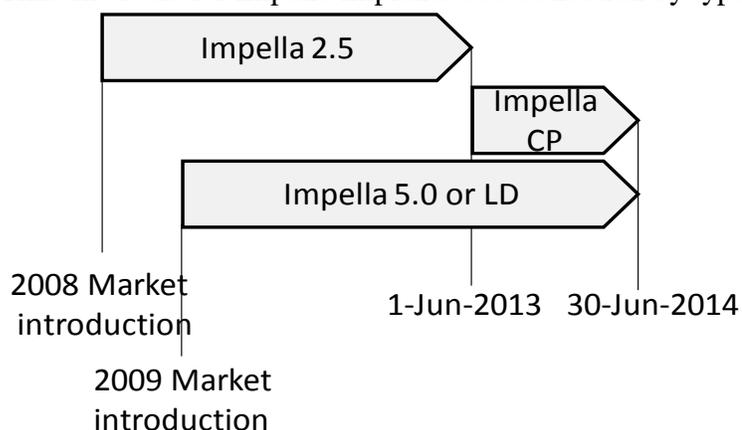
Ventricle (PMA-approved for a similar indication). Clinical data from a separate clinical trial (RECOVER I) was also provided to demonstrate hemodynamic effectiveness of the Impella 5.0/LD device during use. As further evidence, a detailed literature review was also provided to support the overall safety and effectiveness of the Impella devices.

#### **A. Impella Registry**

The Impella Registry is an ongoing, multi-center, retrospective, observational registry for collection of de-identified data for patients treated with the Impella 2.5, Impella CP, Impella 5.0, and Impella LD Support Systems. The registry, which was started by Abiomed in 2009, is open for participation by qualifying sites in the U.S. and Canada. A total 59 sites have participated in the registry since its initiation. As of June 30, 2015, there were 40 open sites. The sites include high and low volume centers, academic (teaching) and non-academic hospitals, public and private institutions as well as for profit and not for profit centers, almost entirely from the United States. Data is collected at all participating sites retrospectively without pre-selection of patients, and included AMICS patients treated with the Impella 2.5, Impella CP, and Impella 5.0/LD Systems. These registry data were used as supplemental informative clinical data for FDA review of the Impella Ventricular Support Systems under P140003/S004, within context of the indications for use.

The data collection from the Impella Registry includes IRB approval, complete data monitoring, adverse events (AEs) monitoring, and CEC adjudication of major AEs. All data is entered electronically by the sites. For this submission, the time during which the Impella Registry data was used is shown in Figure 9. Eligible patients were those who were reported in the Impella Registry as having presented with AMICS and underwent revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and required mechanical circulatory support with Impella devices.

Figure 9: Time intervals for Impella implants data collection by type of device



Cases were initially identified using Abiomed’s commercial patient tracking system, and then further reviewed to verify that each case was applicable for this supplement (i.e., was an AMICS patient). Using this method, three hundred twenty four (324) Impella cases were enrolled into the U.S. Impella Registry for this analysis. These included 189 Impella 2.5 cases, 111 Impella CP cases, and 24 (combined) Impella 5.0 and Impella LD cases.

The data included: patient's demographics and baseline characteristics (risk factors, medical history, and history of previous cardiac interventions), clinical presentation for the index hospitalization, index cardiac procedure information, Impella device information, hemodynamic parameters pre, during and post Impella support, cardiovascular medication, laboratory results, patient's outcome information at discharge and 30-day follow-up, as well as site-reported adverse events. Both site-reported safety data and CEC-adjudicated data are presented.

The data showed that AMICS patients were on average 65 years old, the majority were male (75%) with significant risk factors and comorbidities including smoking (48%), diabetes (42%), hypertension (71%), renal insufficiency (24%), and Society of Thoracic Surgery (STS) scores for mortality of 21% and morbidity of 60%. The patients presented with high heart rate, poor hemodynamics despite pressors and inotropes, signs of tissue hypoperfusion (lactates) and end-organ dysfunction (creatinine). These characteristics were generally the same for all Impella devices, except for: the gender distribution had more male patients in the Impella 2.5 and Impella CP groups (compared to Impella

5.0/LD) and a higher proportion of patients transferred from outlying facilities in patients supported with the Impella 5.0/LD (compared to patients supported with the Impella 2.5 or Impella CP).

In regard to the Impella treatment, the median duration of support was 26 hours for all patients (25 hours for Impella 2.5, 27 hours for the Impella CP, and 69 hours for the Impella 5.0/LD). Overall, the median duration of support was approximately twice as long for survivors. During support, the mean pump flow was 2.3 L/min overall (2.2 L/min for Impella 2.5, 2.9 L/min for Impella CP, and 3.5 L/min for Impella 5.0/LD). The median stay in the intensive care unit (ICU) was 6, 5 and 19 days for the Impella 2.5, Impella CP, and Impella 5.0/LD, respectively. The median duration of hospitalization was 7, 5.5, and 23 days for the Impella 2.5, Impella CP, and Impella 5.0/LD, respectively. The longer durations for the Impella 5.0/LD patients is expected considering their more extensive surgical procedure and generally worse baseline condition.

The overall results for 30-day survival (Kaplan-Meier curve estimates) for the patients are shown in Figure 10. Figure 11 provides the results for the different devices used. The outcome results appear favorable considering the salvage nature of the patient population. Prior to initiation of Impella support, these patients remained in cardiogenic shock after exhausting all conventional measures. Generally, they had failed all recommended therapies, including a short door-to-balloon time for STEMI patients, successful revascularization, and maximum inotropic support with or without IABP.

Figure 10: Kaplan-Meier curve estimates for 30 day survival – All patient cohort

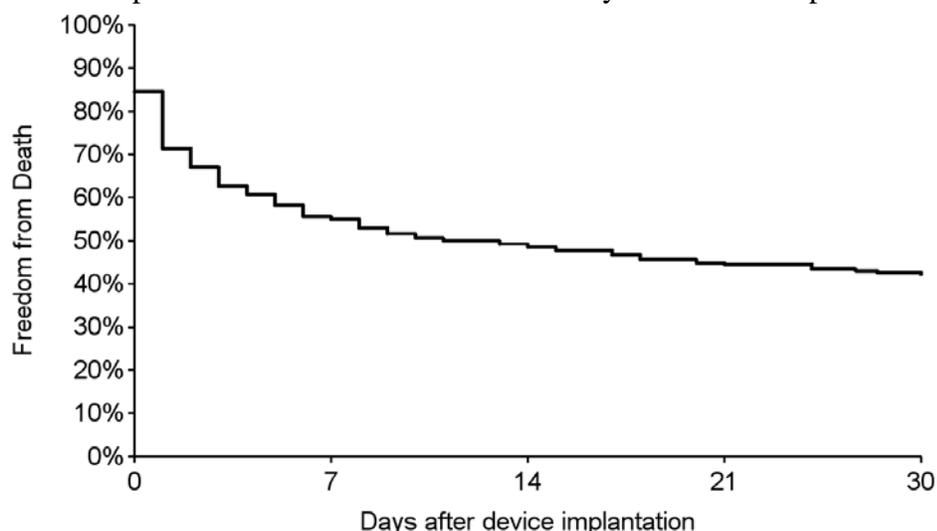
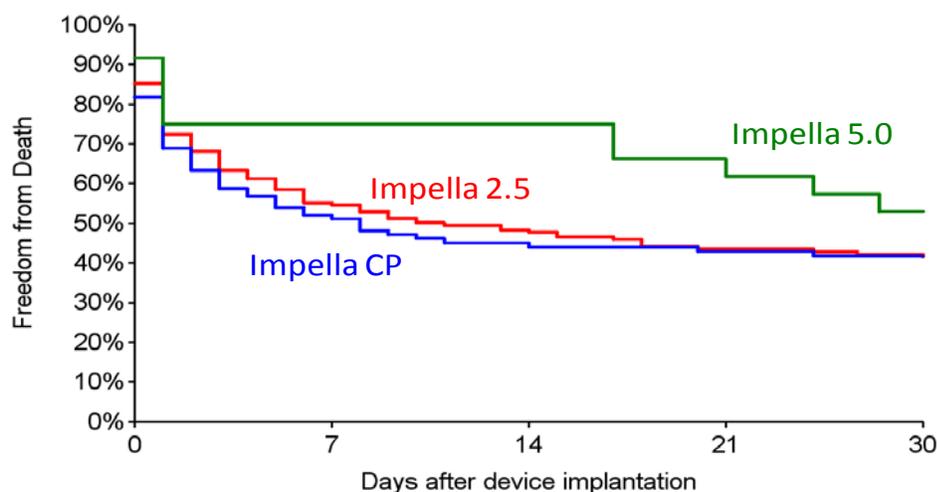


Figure 11: Kaplan-Meier curve estimates, 30 day survival (by device) - All patient cohort



As a further breakdown of the survival outcomes, 29% of the patients expired on Impella device support and 71% were successfully supported to recovery or to next therapy (bridge-to-bridge). In aggregate, 45.7% were discharged (85.8% with recovery, 12.8% transferred to another hospital on Impella support for care management and potential heart transplant or bridge-to-transplant or destination therapy, 1.4% discharged on long-term implantable VAD). By device, 45%, 46%, and 50% of the Impella patients survived to discharge for the Impella 2.5, CP, and 5.0/LD, respectively. There was no observed

difference in outcomes between the different devices, but a trend for better outcomes was seen for patients treated with Impella 5.0/LD (see Figure 11).

#### Additional Analysis of the Impella Registry Data

An additional analysis of different subsets of the Impella Registry patients was provided. The analysis was completed to attempt to evaluate a potential benefit of Impella in a subgroup of the Impella Registry patients, which would be similar to patients selected in prior randomized AMICS RCTs. This was accomplished by dividing the Impella Registry into two groups, a “RCT group” or a group who may have qualified for an AMICS RCT that has been conducted (i.e., SHOCK trial) and a group of “salvage” patients, who would typically be excluded from an AMICS RCT. Specifically, the “salvage patient population” included patients who presented with anoxic brain injury prior to implant, out of hospital cardiac arrest and those who were transferred from an outlying hospital. These higher risk patients would usually be excluded from RCTs because of the time delay in providing care or severity of the insult that makes the shock irreversible despite effective hemodynamic support. The RCT subgroup consisted of 111 patients and the “salvage” subgroup was made up of the remaining 209 patients.

The overall 30-day survival results (Kaplan-Meier curve estimates) for the two subgroups described above are shown in Figure 12. As expected, the “salvage” group of patients has poorer outcomes than the RCT group, which is more representative of patients chosen for AMICS RCTs.

In addition, the outcome data for both 30-day survival and survival to discharge are provided in Figures 13 and 14, respectively, for each Impella device. Interestingly, there appears to be a trend (most noticeable for the RCT group) for an incremental improvement in outcomes with increased flow (from Impella 2.5 to Impella 5.0/LD). This trend reinforces the principle<sup>1</sup> that an increase in the amount of support (cardiac power output) affects outcomes in patients in whom the cardiogenic shock condition is still reversible.

Figure 12: Outcomes between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. Patients likely to be excluded from RCTs (“salvage” patients)

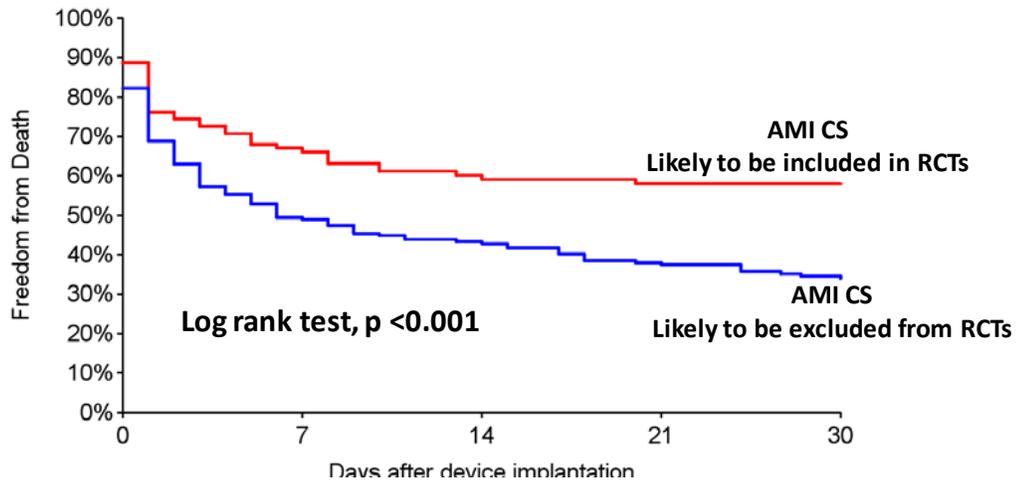


Figure 13: 30-day outcomes (by device) between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. Patients likely to be excluded from RCTs (“salvage” patients)

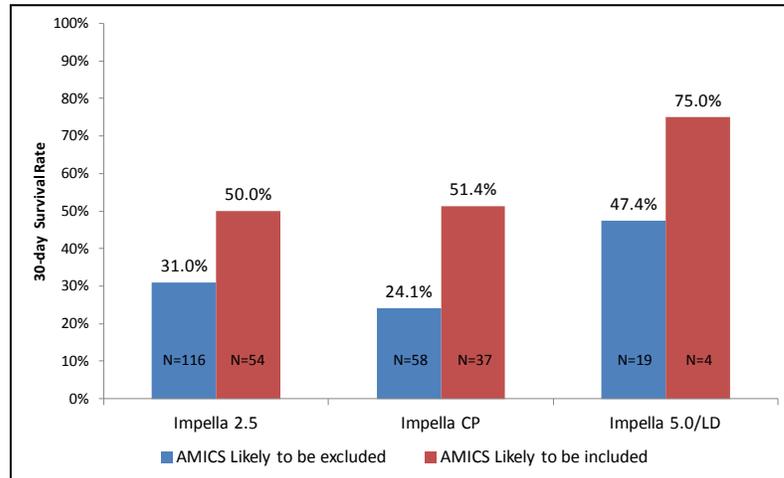
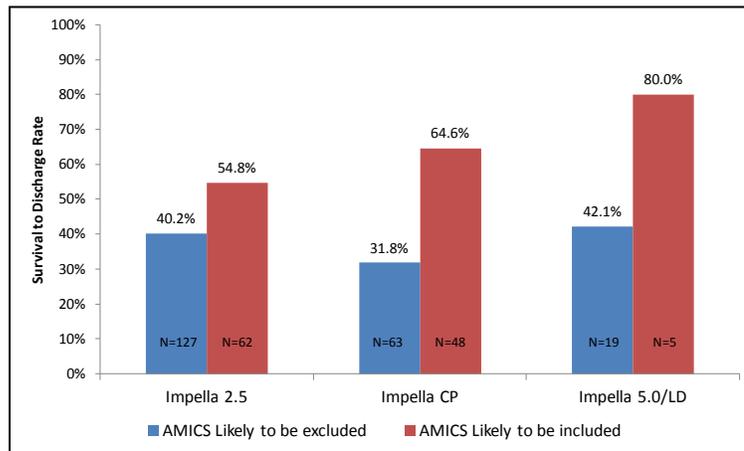


Figure 14: Survival to discharge outcomes (by device) between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. Patients likely to be excluded from RCTs (“salvage” patients)



## B. Benchmarking Impella vs. Approved VAD in AMICS

In order to provide a benchmark for the Impella devices in a comparable clinical setting (AMICS), Abiomed analyzed the results from its real-world registry for the AB5000 Ventricle. The AB5000 Ventricle was PMA approved (P900023/S038) in 2003 as a temporary VAD for use to treat AMICS. The AB5000 Registry was a retrospective registry, which included data collected from U.S. sites between October 3, 2003, and December 11, 2007. The AB5000 Registry included data with demographics, procedural and hemodynamic characteristics, outcomes and adverse events.

The AB5000 Registry includes 2,152 patients. After reviewing the AB5000 Registry and matching the two cohorts (Impella and AB5000 for AMICS), 115 cases from the AB5000 Registry were an eligible match for the benchmark analysis.

The benchmark analysis included the overall survival to 30 days and to discharge in the AMICS patient group. The 30-day Kaplan-Meier estimates are provided in Figure 15. The results are provided for each Impella device. In addition, the survival-to-discharge results are provided in Figure 16.

Figure 15: Kaplan-Meier curve estimates for 30-day survival

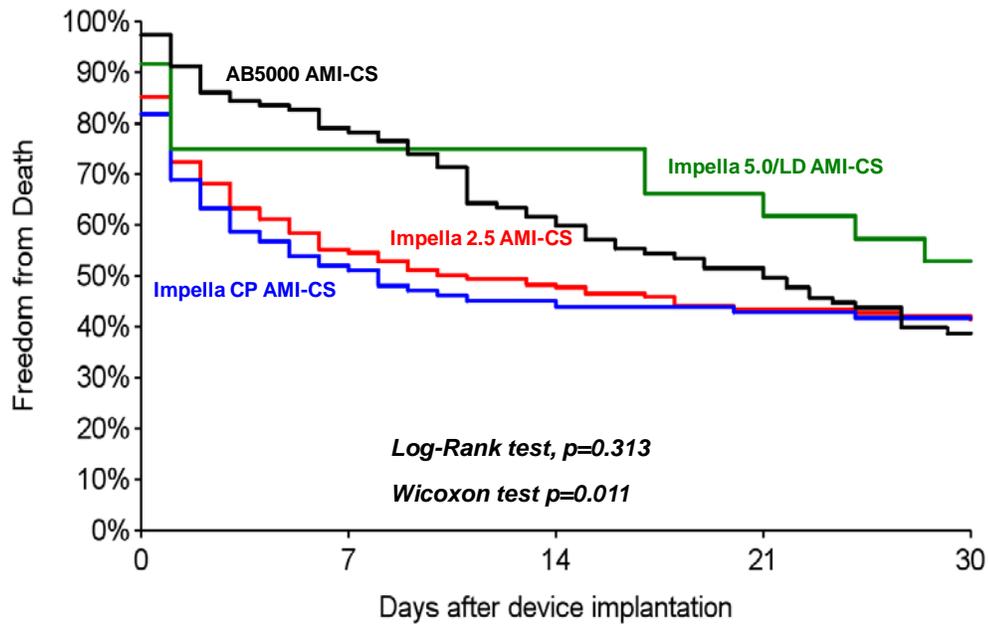
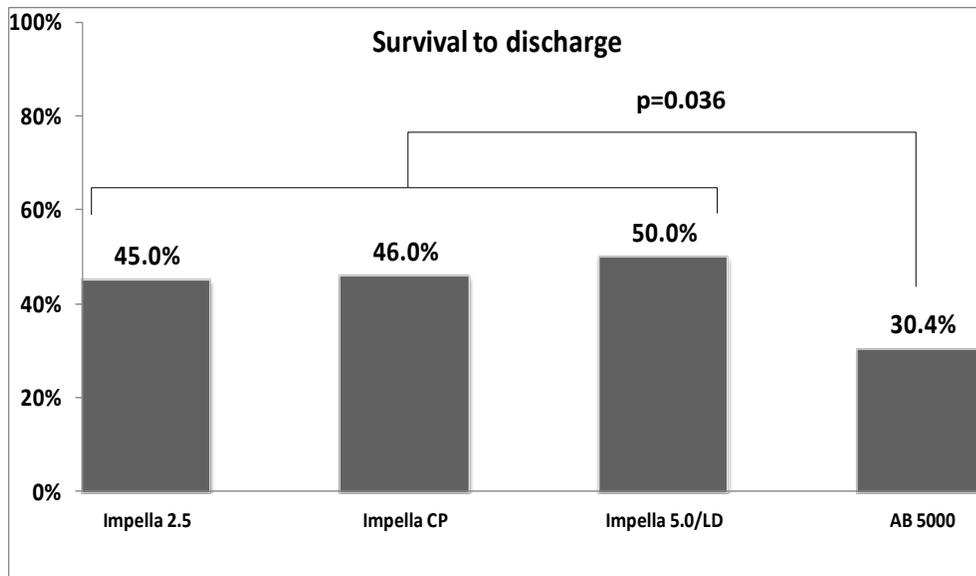


Figure 16: Survival to discharge in AMICS cohort



The trends in the Kaplan Meier curve support the assertion that outcomes are improved when more robust hemodynamic support (i.e., flow) is provided to these hemodynamically compromised patients. Indeed, Impella 5.0/LD and AB5000 initially exhibit the highest survival. However, the data shows that the survival to discharge was

significantly lower in the AB5000 cohort compared to the Impella cohort (30.43% vs. 45.68%,  $p=0.036$ ), even though the AB5000 is the most potent device. For this comparison, the longer duration of support and the invasiveness of the AB5000 likely increases the risk of device-related morbidities as the support is extended. These issues can result in serious complications culminating in death events. Therefore, a potential benefit of the higher hemodynamic support of a surgical VAD is offset by the high complication rates that impair outcomes.

In addition, to assess overall safety of use of the Impella devices, the rates of site-reported in-hospital adverse events were compared. The results of this comparison are provided in Table 7. There are several noteworthy differences between the Impella and AB5000 safety profile.

- The cerebral vascular accident (CVA) and stroke events were significantly higher in the AB5000 cohort compared to the Impella devices, which could be explained by the longer duration of support with the AB5000, and its much larger blood contacting device surface area and areas of stasis in the device that interact with the patient blood compared to the Impella device.
- The bleeding rates differed among the groups. For the Impella 5.0/LD group, only 4 patients underwent percutaneous coronary intervention, with the remainder receiving surgical revascularization (i.e., a CABG procedure). As a result, the bleeding rates were similar between the Impella 5.0/LD and AB5000. These were mainly surgical bleeding. However, the bleeding rates for Impella 2.5 and Impella CP, which were placed percutaneously in AMICS patients undergoing PCI, were much lower compared to the other two groups. There were no device-related bleeding events reported.
- There were also differences in the infection rates, with higher incidence in the Impella 5.0/LD and AB5000 groups. Although infections were reported more frequently for the Impella 5.0/LD, this was most likely due to more rigorous contemporary process of reporting adverse events, including all infections (urinary tract infections, streptococcus throat, etc.) in the Impella Registry. None of the infections was determined to be related to the device.

Table 7: Site-reported adverse events (to discharge) by classification

Adverse Events	Impella 2.5 (N=189)	Impella CP (N=111)	Impella 5.0/LD (N=24)	AB5000/BVS/ AB (N=115)	p-value
Death	55.03% (104/189)	54.05% (60/111)	50.00% (12/24)	69.57% (80/115)	0.036
CVA/Stroke	2.65% (5/189)	3.60% (4/111)	4.17% (1/24)	21.74% (25/115)	<.001
TIA	0.00% (0/189)	0.00% (0/111)	0.00% (0/24)	5.22% (6/115)	0.002
Acute Renal Dysfunction	27.51% (52/189)	31.53% (35/111)	41.67% (10/24)	25.22% (29/115)	0.355
Hemolysis	8.47% (16/189)	10.81% (12/111)	8.33% (2/24)	10.43% (12/115)	0.900
Acute Hepatic Failure	10.58% (20/189)	16.22% (18/111)	12.50% (3/24)	11.30% (13/115)	0.516
Bleeding	19.58% (37/189)	17.12% (19/111)	41.67% (10/24)	37.39% (43/115)	<.001
Infection	17.46% (33/189)	13.51% (15/111)	50.00% (12/24)	26.96% (31/115)	<.001
MSOF	1.59% (3/189)	0.00% (0/111)	4.17% (1/24)	18.26% (21/115)	<.001
Respiratory Dysfunction/Failure	10.05% (19/189)	14.41% (16/111)	41.67% (10/24)	22.61% (26/115)	<.001
Supraventricular Arrhythmia	5.82% (11/189)	6.31% (7/111)	16.67% (4/24)	7.83% (9/115)	0.253
Other	19.58% (37/189)	18.02% (20/111)	41.67% (10/24)	27.83% (32/115)	0.032

*CVA: Cerebrovascular accident; TIA: Transient Ischemic Attack; MSOF: Multi System Organ Failure*

Overall, the benchmark analysis reveals that AMICS patients in the Impella Registry had better outcomes to discharge than the patients in the AB5000 Registry. This is likely due to the increased risk with mortality and morbidity associated with a prolonged support and invasiveness that comes with the AB5000 technology. The comparison also showed that the rates of complications were lower in the U.S. Impella Registry cohort. This may

have been a result of the less invasive approach for insertion and operation, shorter duration of support, ease of use to allow earlier mobilization of patients and a reduced ICU and hospital stay.

### **C. Hemodynamic Effectiveness Results**

The Impella Catheters directly unload the left ventricle (LV) and propel blood forward, from the left ventricle into the aorta, in a manner most consistent with normal physiology. Impella provides both an active forward flow<sup>2,3</sup> and systemic aortic pressure (AOP) contribution,<sup>1,2,4</sup> leading to an effective increase in mean arterial pressure (MAP) and overall cardiac power output (CPO).<sup>1,5</sup> Combined with LV unloading, Impella support reduces end-diastolic volume and pressure (EDV, EDP)<sup>1,2</sup> and augments peak coronary flow,<sup>1,2,6,7</sup> leading to a favorable alteration of the balance of myocardial oxygen supply and demand. This cascade of hemodynamic effects has been described in the literature<sup>8</sup> and validated in computational modeling and a variety of pre-clinical and clinical studies.<sup>1-7</sup>

As initial clinical evidence of the hemodynamic benefits of Impella support, results from a clinical trial with the Impella 5.0 and Impella LD are provided. The study, RECOVER I, was an FDA-approved prospective, single-arm study that evaluated the safety, hemodynamic benefit, and feasibility for the Impella 5.0 and the Impella LD in a post-cardiotomy setting. As part of the study, hemodynamic data was collected at baseline and over time to evaluate the robustness of the hemodynamic support with the Impella 5.0 and Impella LD devices in patients experiencing hemodynamic compromise/cardiogenic shock post-cardiac surgery. Cardiac output (CO), cardiac index (CI), mean arterial pressure (MAP), cardiac power output (CPO), cardiac power index (CPI) and pulmonary artery diastolic blood pressure (PAd) measurements were collected. The data collected showed an immediate improvement of the hemodynamics of post-cardiotomy cardiogenic shock (PCCS) patients post-device implant, as shown in Figure 17. In addition, as patients' hemodynamics improved, a rapid and sustained weaning of inotropic and pressor support was also concomitantly observed, as shown in Figure 18.

Figure 17: Improvement in patient hemodynamics (from baseline to 48hrs post device implant) for RECOVER I patients

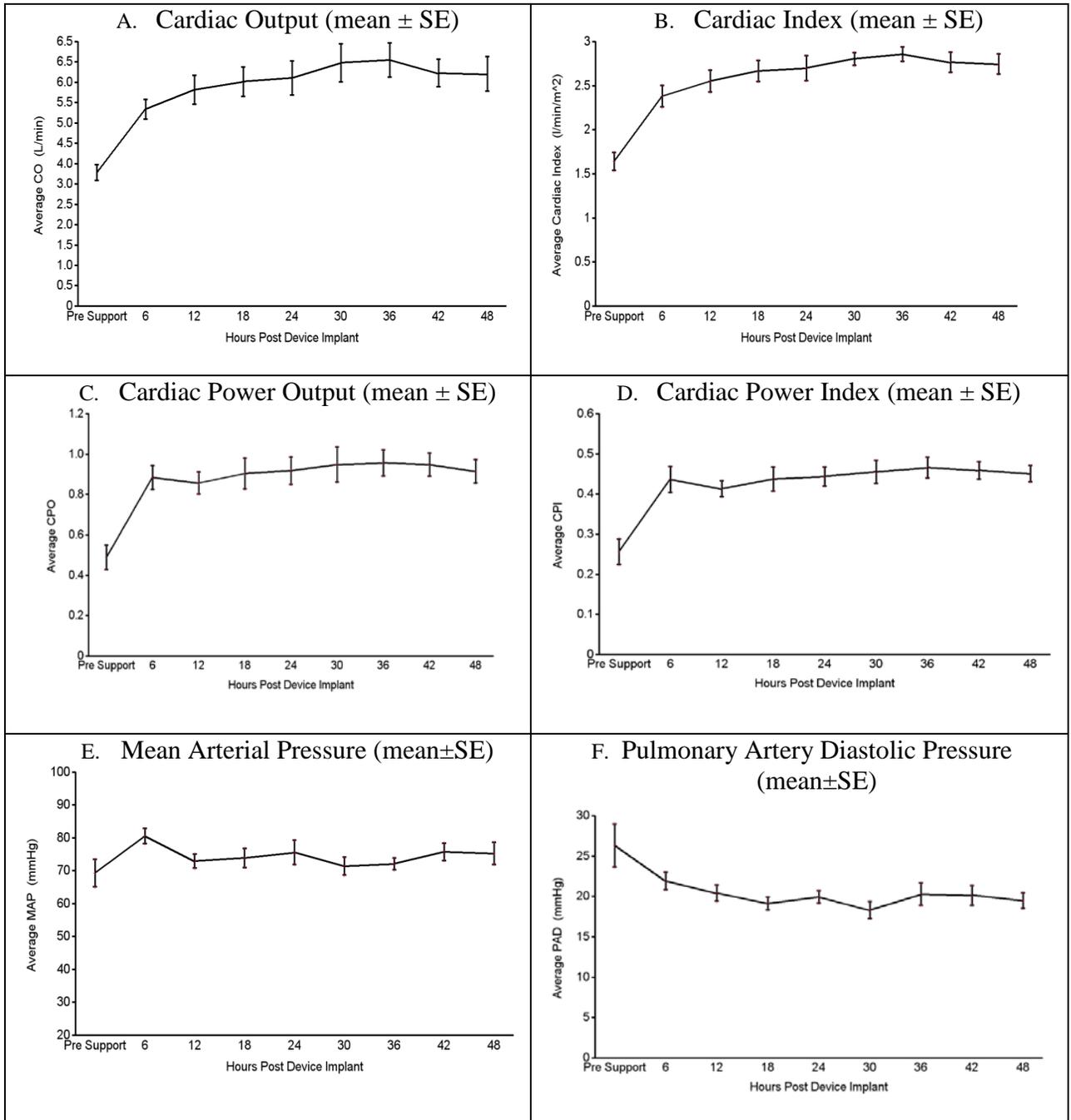
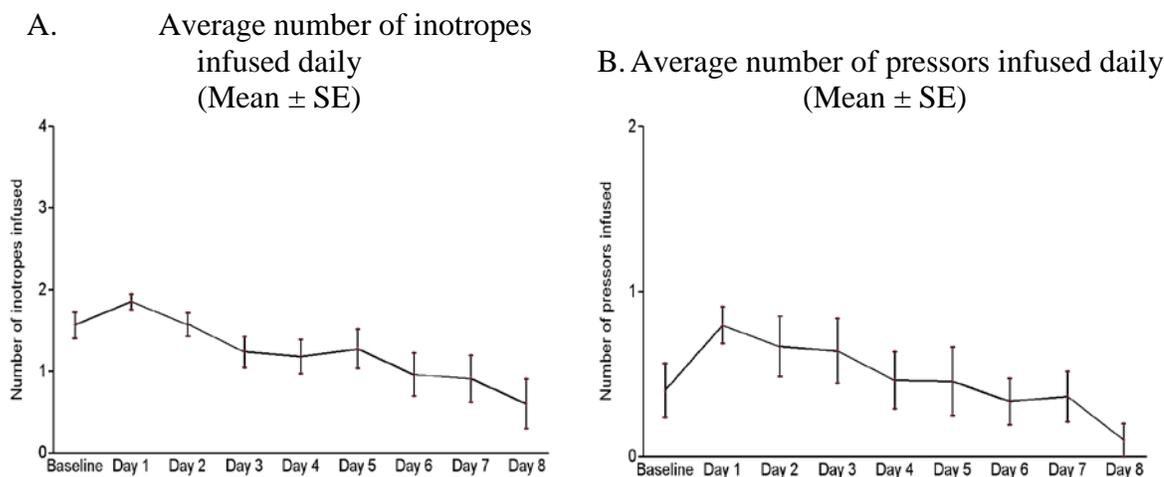


Figure 18: Decrease in inotropes and pressors (post-device placement) for RECOVER I patients



Additional hemodynamic and other clinical data was provided from both an FDA approved prospective randomized study (PROTECT II) and real-world use data to further corroborate the hemodynamic benefits afforded by use of the Impella devices.

#### D. Literature Review

The literature review provided has three components. The first component is a review and characterization of the use of Impella to treat AMICS patients. The second component is a comparison of the results of the Impella literature review to a literature review of Abiomed’s PMA-approved surgical VADs (the BVS and AB5000) in AMICS. The third component is a literature review of the use of extracorporeal membrane oxygenation (ECMO) in this population, since ECMO is used as an alternative device to support these patients as well, albeit off-label.

The Impella review encompassed a large body of scientific evidence with over 315 publications available for review. The filtering of these publications resulted in over 692 patients in 17 publications for the relevant use of Impella devices, which included 469 patients in 9 publications treated for this specific proposed indication for use. The literature review provides further insight into the use of the Impella devices in routine clinical practice.

The literature analysis shows that AMICS patients who are deemed to require emergent hemodynamic support are, in general, older and present with high-risk comorbidities, poor functional status and greatly depressed cardiac function. Overall, the use of Impella devices to support AMICS patients appears to be safe and effective, based on the studies published in the literature. The survival rates and morbidities also appear to be favorable for use of the Impella devices as compared to the surgical VADs.

The review of ECMO in these same patients yielded a mean survival to either discharge of 30 days at 43% (range 29% to 59%) representing 6 studies and over 265 patients. The results of the ECMO review indicate that the use of ECMO, which is a much more invasive system, yielded a higher morbidity profile during support than use of the less invasive Impella devices for a potential comparable or less favorable survival outcome.

Overall, the literature analysis provides further reasonable assurance of safety and effectiveness of the Impella devices in the proposed indications for use.

## **XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Safety Conclusions**

The results from the nonclinical laboratory studies performed on the Impella 2.5, Impella CP, and Impella 5.0/LD demonstrate that the devices are suitable for their intended use. There were no device-related serious adverse events reported with Impella 2.5 in the ISAR-SHOCK study. Investigators reported 1 case of hemolysis, 1 hematoma at the insertion site, and 1 case of bleeding at the insertion

site that required manual compression for 20 minutes. The benchmark analysis comparing the Impella catheters with the AB5000 surgical VAD showed decreases in death, cerebrovascular accident (CVA)/stroke, transient ischemic attack (TIA), bleeding, infection, multi-system organ failure, and respiratory dysfunction/failure.

## **B. Effectiveness Conclusions**

In the AMICS patient population, the primary outcome of interest is survival to discharge. The ISAR-SHOCK study showed comparable survival rates at 30 days to the IABP control. Survival in a salvage AMICS population as recorded in the Impella Registry shows an approximate survival to discharge rate of 45-50%. Historical data from the AB5000 surgical VAD in a similar population show a 30.4% survival to discharge rate.

Additionally, RECOVER I showed improvement in average hemodynamic parameter values (including cardiac output, cardiac index, cardiac power output, cardiac power index, mean arterial pressure, and pulmonary artery diastolic pressure) from baseline to 48 hours post-initiation of support with the Impella 5.0/LD. ISAR-SHOCK showed hemodynamic improvement (improvement in cardiac index) within the first 60 minutes after insertion of the Impella 2.5 compared to the IABP control.

Other clinical benefits may include decrease in inotropic usage, as demonstrated in RECOVER I and ISAR-SHOCK, and high rates (85.81%) of recovery (i.e., discharge of the patient with native unassisted heart function) among AMICS survivors as reported by the Impella Registry.

In conclusion, given the totality of the information available for the Impella Ventricular Support Systems, the data demonstrate a beneficial therapeutic effect in patients experiencing AMICS.

**C. Benefit-Risk Conclusions:**

Patients experiencing AMICS in need of circulatory support due to ongoing cardiogenic shock refractory to other available therapies are exposed to imminent risk of mortality if hemodynamic support that results in augmentation of cardiac output is not provided.

The probable benefits of the device as compared to other available treatments such as IABP or surgical VADs include potential improved survival, improved hemodynamic support, reduction in use of inotropes, and a high heart recovery rate in survivors.

The probable risks of the Impella Ventricular Support Systems in this patient population were evaluated using the ISAR-SHOCK study and the supportive data from the Impella Registry. The safety profile was favorable compared with other approved VADs. Risks of bleeding and the need for transfusion in general remain high, mainly driven by the patient's general situation (not device-related), but are numerically lower than other surgical VADs. Because most of the risks were deemed to be procedure-related, results may improve with training.

The benefit-risk evaluation is favorable for use of the Impella 2.5, Impella CP, and 5.0/LD as temporary ventricular support devices to support hemodynamics and augment the circulation in patients who are suffering from AMICS where other standard therapies (pressors, inotropes, IABP) have failed.

**D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

#### **XIV. CDRH DECISION**

FDA issued an approval order on April 7, 2016.

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

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

**OSB Lead PMA Post-Approval Study - Impella AMI CS PAS** This PAS will be an observational clinical investigation of patients indicated for receipt of an Impella device that suffered cardiogenic shock after an acute myocardial infarction. A minimum of 276 participants will be evaluable to compare the survival rate at 30 days or discharge, whichever is longer, to a performance goal of 34%. It is estimated that 304 participants will be enrolled, assuming 10% loss to follow-up to 30 days post-procedure. In addition to survival rates, information on technical success at exit from the catheterization lab or operating room, device and patient success, descriptions of adverse events through three months follow-up (as well as one year, when available) and the adverse event rate at 30 days or discharge, whichever is longer, will be provided.

#### **XV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling (Instructions for Use).

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

Post-approval Requirements and Restrictions: See Approval Order.

## **XVI. REFERENCES**

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