## SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

### I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | A temporary non-roller type cardiac support blood pump. |
| Device Trade Name: | Impella 2.5 System |
| Device Product Code: | OZD |
| Applicant Name and Address: | ABIOMED, Inc.<br>22 Cherry Hill Drive<br>Danvers, MA 01923 |
| Date of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P140003 |
| Date of Notice of Approval to Applicant: | March 23, 2015 |

### II. INDICATIONS FOR USE

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 System 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.

### 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 $cm^2$ or less)
- Moderate to severe aortic insufficiency (echocardiographic assessment graded as ≥ +2)
- Severe peripheral arterial disease precluding placement of the Impella® 2.5 System

### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the approved labeling for the Impella 2.5 System.

## V. DEVICE DESCRIPTION

The Impella 2.5 System is comprised of three components manufactured by ABIOMED:

- Automated Impella Controller (AIC), a reusable extracorporeal drive console
- Impella 2.5 Catheter, a 12F micro-axial rotary blood pump mounted on a 9F catheter
- Impella Purge Cassette, an infusion pump used to flush the Impella 2.5 Catheter.

The AIC (shown in Figure 1) controls both the Impella 2.5 Catheter and the Impella Purge Cassette. It is a durable (reusable) driver. The Impella 2.5 Catheter and the Impella Purge Cassette (shown in Figure 2) are sterile, single use products.

Figure 1: AIC with an Impella 2.5 Catheter (left) and an Impella Purge Cassette (right)

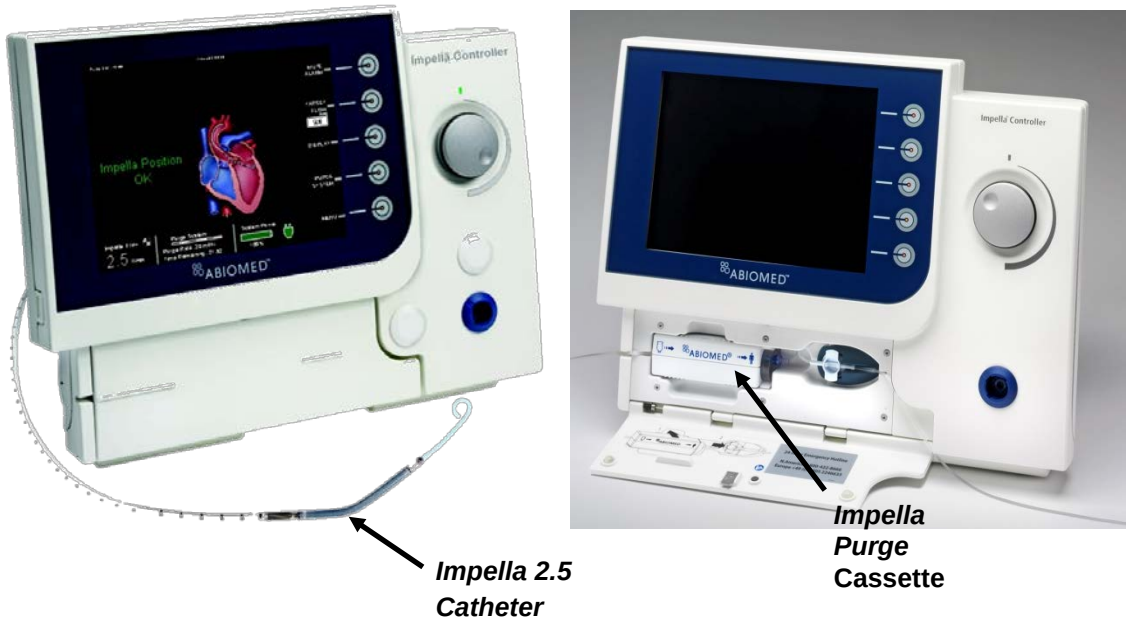
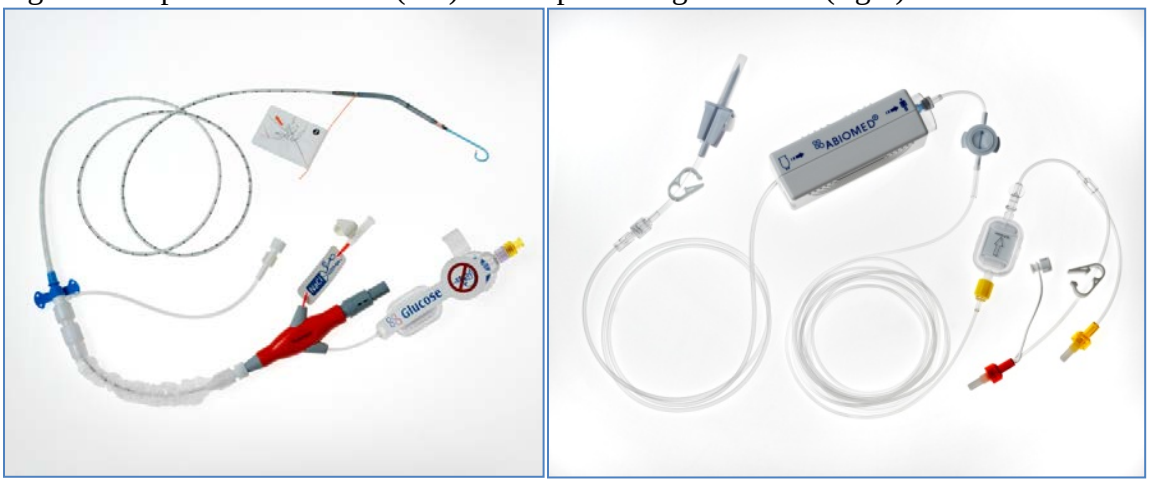
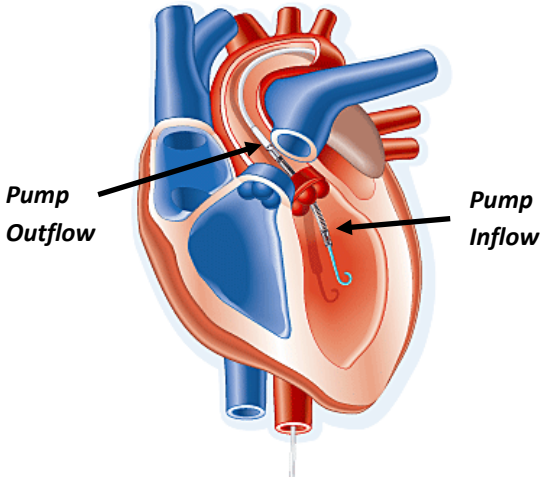



Figure 2: Impella 2.5 Catheter (left) and Impella Purge Cassette (right)



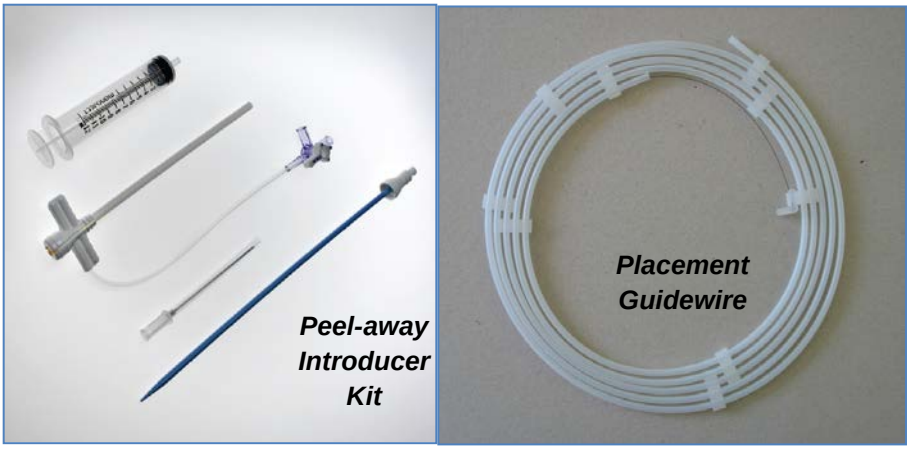
The Impella 2.5 System is a minimally invasive, miniaturized percutaneous circulatory support system that is placed across the aortic valve via a single femoral arterial access. The Impella 2.5 Catheter consists of a micro-axial rotary blood pump mounted on a 9F catheter. The Impella 2.5 Catheter can be percutaneously inserted through the femoral artery and positioned across the aortic valve into the left ventricle. The device actively unloads the left ventricle by pumping blood from the ventricle into the ascending aorta and systemic circulation (shown in Figure 3). When in place, the Impella 2.5 Catheter can be driven by the AIC to provide up to 2.5 liters/minute of partial left ventricular support. This is accomplished by drawing blood out of the ventricle and pumping it across the aortic valve into the ascending aorta.

Figure 3: Impella 2.5 Catheter placement during use




Two additional sterile, disposable accessories (shown in Figure 4) are provided with the Impella 2.5 Catheter to assist in its percutaneous insertion. These components are original equipment manufacturer (OEM) components, a 13 F Peel-away Introducer kit (manufactured by Merit Medical) and a 0.018" placement guidewire (manufactured by Lakes Region Medical).

Figure 4: Disposable 510(k) cleared accessories, which are packaged with the Impella 2.5 Catheter.



A reusable cart for the AIC is also provided with the Impella 2.5 System, to provide ease of patient transport within the hospital.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative to the Impella 2.5 System for patients undergoing high-risk procedures who are at high risk for hemodynamic instability due to planned procedure-related interruption of coronary flow that may lead to hemodynamic compromise and complications includes prophylactic or hemodynamically indicated intra-aortic balloon pump (IABP) counterpulsation therapy.

## VII. MARKETING HISTORY

The Impella 2.5 System has received its CE Mark in the European Union (EU) as well as approval in Canada for a similar intended use during high risk percutaneous coronary interventions (PCI). In the U.S., the Impella 2.5 System was cleared for sale via a pre-market notification (510(k)) as a non-roller-type cardiopulmonary bypass blood pump (Class KFM, Regulation Number 870.4360) in 2008. The Impella 2.5 System has not 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 2.5 System in patients undergoing high Risk PCI (*for the specific adverse events that occurred during the clinical study, please refer to Section X below*):

- 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

## IX. SUMMARY OF PRECLINICAL STUDIES

### A. Laboratory Testing

In vitro studies were performed for the Impella 2.5 System, including its disposable components, the Impella 2.5 Catheter and the Impella Purge Cassette, and their durable drive console, the AIC. 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 2.5 System.

Biocompatibility Studies

Toxicology and biocompatibility tests for the Impella 2.5 System components 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.

Summaries of the test results for the Impella 2.5 Catheter and Impella Purge Cassette are provided in Tables 1 and 2, respectively. Test samples for the studies consisted of all patient-contacting portions of the manufactured devices (direct and indirect blood contacting) after sterilant exposure. All results were found to be acceptable.

Table 1: Summary of biocompatibility testing – Impella 2.5 Catheter

| Test | Date | Standards Referenced | Result |
|---|---|---|---|
| Cytotoxicity & Leachability | 06/22/2011<br>10/05/2011 | ISO 10993-5<br>ISO 10993-18 | Passed |
| Irritation | 07/30/2010 | ISO 10993-10 | Passed |
| Sensitization | 07/06/2010 | ISO 10993-10 | Passed |
| Acute systemic toxicity | 07/30/2010 | ISO 10993-11 | Passed |
| Genotoxicity | 08/24/2010<br>10/20/2010 | ISO 10993-3 (AMES Test)<br>ISO 10993-3 (Chromosomal) | Passed |
| Pyrogen | 08/27/2010 | ISO 10993-11 | Passed |
| Activated Partial Thromboplastin Time (PTT) | 12/19/2006 | ISO 10993-4 (Direct Blood Contact) | Passed |
| Prothrombin Time (PT) | 12/19/2006 | ISO 10993-4 (Direct Blood Contact) | Passed |
| Hemolysis | 01/24/2014 | ISO 10993-4 (Direct Blood Contact)<br>ISO 10993-4 (Indirect Blood Contact)) | Passed |

Table 2: Summary of biocompatibility testing – Impella 2.5 Purge Cassette

| Test | Date | Standards Referenced | Result |
|---|---|---|---|
| Cytotoxicity | 08/13/2010 | ISO 10993-5 | Passed |
| Irritation | 08/27/2010 | ISO 10993-10 | Passed |
| Sensitization | 09/16/2010 | ISO 10993-10 | Passed |
| Acute systemic toxicity | 09/03/2010 | ISO 10993-11 | Passed |
| Pyrogen test | 08/27/2010 | ISO 10993-11 | Passed |
| Hemolysis | 01/24/2014 | ISO 10993-4 (Indirect Blood Contact) | Passed |

Structural Integrity Testing

Structural tests of the Impella 2.5 System components were conducted. Summaries of the test results for the Impella 2.5 Catheter and Impella Purge Cassette are given in Table 3.

Table 3: Summary of Impella 2.5 System safety testing

| Test | Description | Result |
|---|---|---|
| **Impella 2.5 Catheter** | | |
| Bend | This test verified that the Impella 2.5 Catheter could survive the bending stresses expected during its clinical use. | Passed |
| Tensile | This test verified that the Impella 2.5 Catheter joints all exceeded their minimum acceptable tensile strength compatible with its use. | Passed |
| Pump Temperature | This test verified that the maximum external temperatures of the Impella 2.5 Catheter were acceptable for clinical use. | Passed |
| Fluid Tightness (Introducer) | This test verified that the 13 F introducer was compatible with the internal pressures expected during its use. | Passed |
| **Impella Purge Cassette** | | |
| Tensile | The test verified that the Impella Purge Cassette withstood the expected tensile forces expected during its use. | Passed |
| Fluid Tightness (Purge System) | This test verified that the Impella Purge Cassette withstood the internal pressures required during use. | Passed |

Electrical Compatibility, Immunity Standards & Safety Testing

The Impella 2.5 System (the Impella 2.5 Catheter, the Automatic Impella Controller (AIC), and the Impella Purge Cassette) was tested for Electromagnetic Compatibility (EMC), Electromagnetic Immunity (EMI), & Electrical Safety against the relevant national and international standards. Testing verified compliance to recognized FDA Standards, including to IEC 60601-1, 2nd and 3rd editions. Where applicable, testing was also performed in accordance with IEC 60601-1-2 *Issued: 2007 (*3rd edition*).* All of the EMC, EMI & Electrical Safety tests passed.

Performance Testing

Performance tests for the Impella 2.5 Catheter, AIC and Impella Purge Cassette were conducted. Summaries of the test results are given in Table 4.

Table 4: Summary of Impella 2.5 System performance testing

| Test | Description | Result |
|---|---|---|
| **Impella 2.5 Catheter** | | |
| Flow Characterization | This test verified acceptable flow accuracy (determined by comparing the displayed flow rate to a calibrated flow meter). | Pass |
| Simulated Placement & Cannula Kink | This test verified the device can be placed using a peripheral technique, and had acceptable kink resistance for clinical use. | Pass |
| Marker Band Radiopacity | The test verifies that the cannula marker is visible under fluoroscopy per ASTM F640. | Pass |
| Computer Fluid Dynamics (CFD) | CFD was performed to investigate the flow design for the potential low pressure or high shear zones the device. | Pass |
| Hemolysis Tests | To demonstrate that the hemolysis levels associated with the Impella 2.5 System are acceptable when used as intended | Pass |
| **AIC** | | |
| Full System Performance | To verify that the performance/ compatibility of the AIC with the Impella 2.5 Catheter provides the needed pressure and flows for circulatory support for expected | Pass |

| | | |
|---|---|---|
| | clinical scenarios. | |
| Sensor Response | This test verified that the AIC can display the pump pressures accurately (at acceptable response frequencies). | Pass |
| System Characterization | This test verified the purge flow characteristics of the Impella 2.5 System were acceptable for the limits of its operating ranges (i.e. of the catheter and the purge system). | Pass |
| Battery Charge/ Discharge | To verify that the AIC is capable of running a device on the rechargeable Li-ion batteries for 90 minutes and that the system is capable of charging the batteries (once discharged). | Pass |
| Thermal Stress | To verify that the AIC can function properly at its upper temperature limit. | Pass |
| **Impella Purge Cassette** | | |
| Flow Accuracy | To verify the AIC's purge system provides acceptable purge fluid flow (response & accuracy) over its operating range. | Pass |
| Pressure Accuracy | To verify the AIC's purge system provides acceptable purge pressure readings over its operating range. | Pass |

Reliability Testing

Reliability tests of the Impella 2.5 System components were conducted. Summaries of the test results for the Impella 2.5 Catheter, AIC and Impella Purge Cassette are given in Table 5.

Table 5: Summary of Impella 2.5 System reliability testing

| Description | Result |
|---|---|
| **Impella 2.5 Catheter** | |
| This test verified that the Impella 2.5 Catheter has acceptable reliability for its intended duration of use | Pass |
| **AIC** | |
| This test verified that the AIC has an acceptable reliability & validated its planned service interval (for up to 1 year of use). | Pass |
| **Impella Purge Cassette** | |
| This test verified that the Impella Purge Cassette has acceptable reliability for its intended duration of use | Pass |

Patient Transport Testing

The Impella 2.5 System was also tested for compatibility with patient transport between hospitals by trained healthcare professionals (i.e. by ambulance, helicopter, or fixed-wing aircraft) environments. Intra-hospital transport may be required if a patient requires additional resources and specialized teams located at another hospital. These needs may be based on the need for prolonged hemodynamic support which may occur as an unintended consequence of the inability to wean the patient from what was intended to be temporary support (<6 hours). The patient may be transferred to such a location using the Automated Impella® Controller for hospital-to-hospital transport via ambulance, helicopter, or fixed-wing aircraft. Summaries of the transport test results for the Impella 2.5 System are given in Table 6. The test results are compatible with this use scenario.

Table 6: Summary of Impella 2.5 System transport testing

| Test | Description | Result |
|---|---|---|
| Vibration | The testing qualified the AIC for vibration levels for helicopter transport (DOT-C 160-C). | Pass |
| Altitude | The testing qualified the AIC performance at the altitude conditions seen during air transport. | Pass |
| Performance to Specified Power Sources | The testing qualified the AIC for A.C. power, A.C. inverter power & emergency vehicle battery power for patient transport. | Pass |
| Temperature & Humidity | The testing qualified the AIC for operation over a temperature & humidity range pertinent to patient transport. | Pass |

Software Verification & Validation-

The AIC is controlled by proprietary software designed and validated by ABIOMED. Software (SW) design and testing was conducted in compliance with the FDA 2005 document titled "Guidance for Industry and FDA Staff- Guidance for the Content of Pre-market Submissions for SW Contained in Medical Devices" (issued on May 11, 2005). The software development process also complies with the requirements lEC 6060-1-4:1996.

Verification & Validation (V&V) testing was performed using the latest SW version. The SW Verification test results demonstrated that all of the SW requirements for the AIC were met in the current product design. The SW Validation tests results demonstrated that the Impella 2.5 System performed as intended with the latest version of the SW. Any anomalies remaining after the V&V testing were evaluated and determined to be minor in severity, and have no potential clinical impact.

Hazard Analysis

Potential hazards associated with the Impella 2.5 System, 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 its 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. Impella 2.5 System Animal Studies

Two chronic animal studies were completed with the Impella 2.5 System.

An initial chronic animal study was completed in 2004, which demonstrated survival in an ovine model on an early version of the Impella 2.5 System, which included a prior design of the Impella 2.5 Catheter, a first generation of the Impella pump controller, and a separate commercially available purge system. The study was completed under a pre-approved protocol. This study demonstrated safety and feasibility of use of the Impella 2.5 System, and was provided in the original IDE application (for G050017).

A second chronic animal study was completed in 2010, in a bovine model, and evaluated the current Impella 2.5 System, including the Impella 2.5 Catheter, the AIC and the Impella Purge Cassette. The study was completed under a pre-approved protocol, and pre-specified primary and secondary endpoints for safety and efficacy were evaluated. All of the primary endpoints were met. The secondary endpoints, which were designed to evaluate the AIC usability, were generally met, but a few (primarily related to the long term placement of the device) were confounded by the high mobility associated with the animal model. Overall, the study further validated that the Impella 2.5 System could be used safely without causing any adverse reactions or unexpected product performance failures or malfunctions.

### C. Sterilization

The Impella 2.5 Catheter and the Impella Purge Cassette are both sterilized. The sterilization method is 100% ethylene oxide (EO), and the sterilization process is validated to provide a sterility assurance level (SAL) of $10^{-6}$ in accordance with international standards for sterilization processes for medical devices, ANSI/AAMI/ISO 11135:1994, 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 the Impella 2.5 Catheter and Impella Purge Cassette. All tests passed.

### E. Package Integrity

Package integrity testing was completed for each of the Impella 2.5 System components. Summaries of the test completed are provided in Table 7.

Table 7: Summary of Impella 2.5 System package integrity testing

| Test | Description | Result |
|---|---|---|
| **Impella 2.5 Catheter** | | |
| Package Test: Seal Integrity | This test verified that the Impella 2.5 Catheter's package seals have acceptable:<br>1) strength (tensile test)<br>2) integrity (dye penetration test). | 1) Pass<br>2) Pass |
| Package Test: Shipping | This test verified that that the Impella 2.5 Catheter's packaging will provide adequate protection for shipment (ISTA 2A Standard). | Pass |
| **AIC** | | |
| Package Test: Shipping & Transport | This test verified that the AIC packaging will provide adequate protection for shipment. (ISTA 2A Standard). | Pass |
| **Impella Purge Cassette** | | |
| Package Tests: Seal Strength & Integrity | This test verified that the Impella Purge Cassette's package seals have acceptable:<br>1) strength (tensile test),<br>2) integrity (dye penetration test). | 1) Pass<br>2) Pass |
| Package Test: Shipping | This test verified that that the Impella Purge Cassette's packaging will provide adequate protection for shipment (ISTA 2A Standard). | Pass |

## X. SUMMARY OF PRIMARY CLINICAL STUDIES

The totality of the US human clinical data includes an initial safety study (PROTECT I), a multi-center, prospective, randomized controlled clinical trial (PROTECT II) and data from a retrospective registry, USpella, along with a literature review. This section is focused primarily on PROTECT II, conducted under IDE # G050017 Data from this clinical trial and the other data are the basis for the PMA approval decision.

Table 8: Summary of primary clinical studies

| Clinical Study | Study Design | Objective | Number of Sites | Number of Subjects |
|---|---|---|---|---|
| PROTECT I | Prospective, multi-center, single arm, study | To examine the safety and feasibility of Impella 2.5 System in patients undergoing high risk angioplasty procedures | 7 | 20 patients enrolled and available for 30 day follow up |

| | | | | |
|---|---|---|---|---|
| PROTECT II | Prospective, multi-center, randomized controlled trial | To assess the safety and efficacy of the Impella 2.5 System compared to intra-aortic balloon pump when used in subjects undergoing non-emergent high risk PCI | 112 | 452 patients enrolled; 448 patients in Intent-to-Treat population; 427 patients in Per-Protocol population |
| USpella Registry | Retrospective, multi-center voluntary registry | To examine the safety and effectiveness of the Impella 2.5 System when used in routine clinical practice for high risk PCI | 49 | 637 patients in high risk PCI cohort |

**PROTECT I Clinical Study**

PROTECT I was a prospective, single arm, multi-center feasibility study designed under FDA guidance to examine the safety and feasibility of Impella 2.5 System in patients undergoing high risk angioplasty procedures. Patients presenting with a left ventricular ejection fraction (LVEF) ≤35% and scheduled to undergo PCI on an unprotected left main lesion or last patent conduit were considered for enrollment. Safety endpoints included 30 day rate of major cardiac and cerebral events (MACCE) and other vascular, thromboembolic, and hemorrhagic safety endpoints. Efficacy endpoints included hemodynamic benefit and freedom from intra-procedural ischemia driven ventricular fibrillation or tachycardia requiring cardioversion. The study showed an excellent safety profile of the device when used as temporary ventricular support in high risk PCI. The FDA reviewed this data in consideration for approval of the PROTECT II trial based on PROTECT I meeting its primary and secondary endpoints.

**PROTECT II Pivotal Clinical Study Design**

**A. Study Design**

The main clinical study (PROTECT II) was a prospective, multi-center, randomized, open label, active controlled clinical study. The objective of the PROTECT II study was to assess the safety and efficacy of the Impella 2.5 System compared to the intra-aortic balloon pump (IABP) when used in subjects undergoing non-emergent high risk PCI. The hypothesis of the study was to demonstrate that prophylactic use of Impella 2.5 System was superior to IABP in preventing intra- and post-procedural major adverse events (MAE) in this patient population.

The pre-specified primary endpoint was a composite clinical endpoint of major adverse events (10 component major adverse event [MAE] rate) through 30 days or hospital discharge, whichever was longer, following the PCI procedure. The outcomes were to be compared to the control group treated with an intra-aortic balloon pump (IABP). To assess the durability of potential benefit (i.e., the primary endpoint), the same 10 component MAE rate was also evaluated at 90 days.

The secondary safety endpoints were the same 10 individual components of the composite primary clinical endpoint. Specifically, these were:

1. Death
2. Stroke/TIA
3. Myocardial infarction
4. Repeat revascularization
5. Need for cardiac operation or thoracic or abdominal vascular operation or vascular operation for limb ischemia
6. Acute renal dysfunction
7. Cardiopulmonary resuscitation or Ventricular arrhythmia requiring cardioversion
8. Increase in aortic insufficiency by more than one grade
9. Severe hypotension, defined as: systolic blood pressure or augmented diastolic pressure (whichever is greater) <90 mmHg for ≥5 min requiring inotropic/pressor medications or IV fluid
10. Failure to achieve angiographic success defined as residual stenosis <30% after stent implantation.

Follow-up assessments were performed at 30 days or at discharge (whichever was longer), and at 90 days following the PCI procedure.

There were four secondary effectiveness endpoints:

1. Maximum cardiac power output (CPO) decrease from baseline. CPO was defined as the product of simultaneously measured cardiac output (CO) and mean arterial pressure (MAP). The hypothesis was that the Impella 2.5 System is superior to IABP in preserving hemodynamic status, defined by a lesser degree of CPO decrease during the high risk PCI procedure.
2. Creatinine clearance within 24 hours post procedure
3. Failure of the Impella 2.5 System to maintain a pump output of > 1.0 L/min for more than five minutes while at a performance level P5 or higher in the Impella patients during the procedure
4. Failure of the IABP to augment diastolic pressure above the peak systolic pressure for more than five minutes in the IABP patients.

External Evaluation Groups

The study was sponsored by ABIOMED. The sponsor contracted with Harvard Clinical Research Institute ("HCRI"), an academic research organization to provide study management activities including randomization via Interactive Voice Recognition System (IVRS), site management, site monitoring, data management, statistical analysis, and

oversight of safety processes including the Data Safety Management Board (DSMB) and the Clinical Events Committee (CEC).

The study included two independent Core Labs: Beth Israel Deaconess Medical Center Angiographic Core Laboratory, Boston M.A. for angiographic analyses and Duke Clinical Research Institute, Durham N.C. for echocardiographic analyses. The study protocol was approved by the sponsor, HCRI and the FDA. The protocol pre-specified an interim analysis with stopping rules and a Statistical Analysis Plan (SAP).

Pre-specified Statistical Analysis Plan

The pre-specified study hypothesis was that the Impella 2.5 System would be superior to IABP in reducing the composite rate of intra- and post-procedural major adverse events (MAEs) at 30 days or hospital discharge, whichever is longer post index procedure.

The IABP also was the *only* 510k cleared FDA device for cardiac support for high risk PCI indication. Therefore, the IABP was chosen as the control device for PROTECT II.
The protocol stipulated that the detailed classification and description of the subgroup variables would be defined in the SAP. The following 4 subgroups were pre-specified in the SAP:

1. Assessment of any potential learning curve effect: Evaluate the primary endpoint with and without the first Impella case at each site in order to assess the impact of the learning curve for the protocol and for use of the device.
2. Assessment of the primary endpoint for procedural characteristics or adjunctive therapies not equivalent between the two arms (i.e. rotational atherectomy).
3. Assessment of the primary endpoint stratified by angioplasty indication (last remaining vessel/left main vs. triple vessel disease).
4. Assessment of the primary endpoint stratified by the severity of the patient using the STS mortality risk score.

Clinical Inclusion and Exclusion Criteria

Patients enrolled in PROTECT II were considered at high risk for hemodynamic instability during non-emergent percutaneous coronary intervention due to a combination of depressed left ejection fraction and complex coronary lesions and deemed to require prophylactic hemodynamic support by the treating physician. Patients were required to meet all inclusion criteria and none of the exclusion criteria in order to be enrolled in PROTECT II.

*Inclusion Criteria*

1. Signed Informed Consent
2. Subject is indicated for a non-emergent percutaneous treatment of at least one *de novo* or restenotic lesion in a native coronary vessel or bypass graft

3. Age eligible ($18 \leq Age \leq 90$)
4. Subject presents with:

   a) Ejection Fraction $\leq 35\%$ AND at least one of the following criteria:

      - Intervention on the last patent coronary conduit, or
      - Intervention on an unprotected left main coronary artery

      Or

   b) Ejection Fraction $\leq 30\%$ and intervention in patient presenting with triple vessel disease.

   Three-vessel or triple vessel disease was defined as at least one significant stenosis (i.e. $\geq$ 50% stenosis by diameter) in all three major epicardial territories: left anterior descending artery (LAD) and/or side branch, left circumflex artery (LCX) and/or side branch, and right coronary artery (RCA) and/or side branch. In the case of left coronary artery dominance, a lesion in the LAD and the proximal LCX qualified as three-vessel disease.

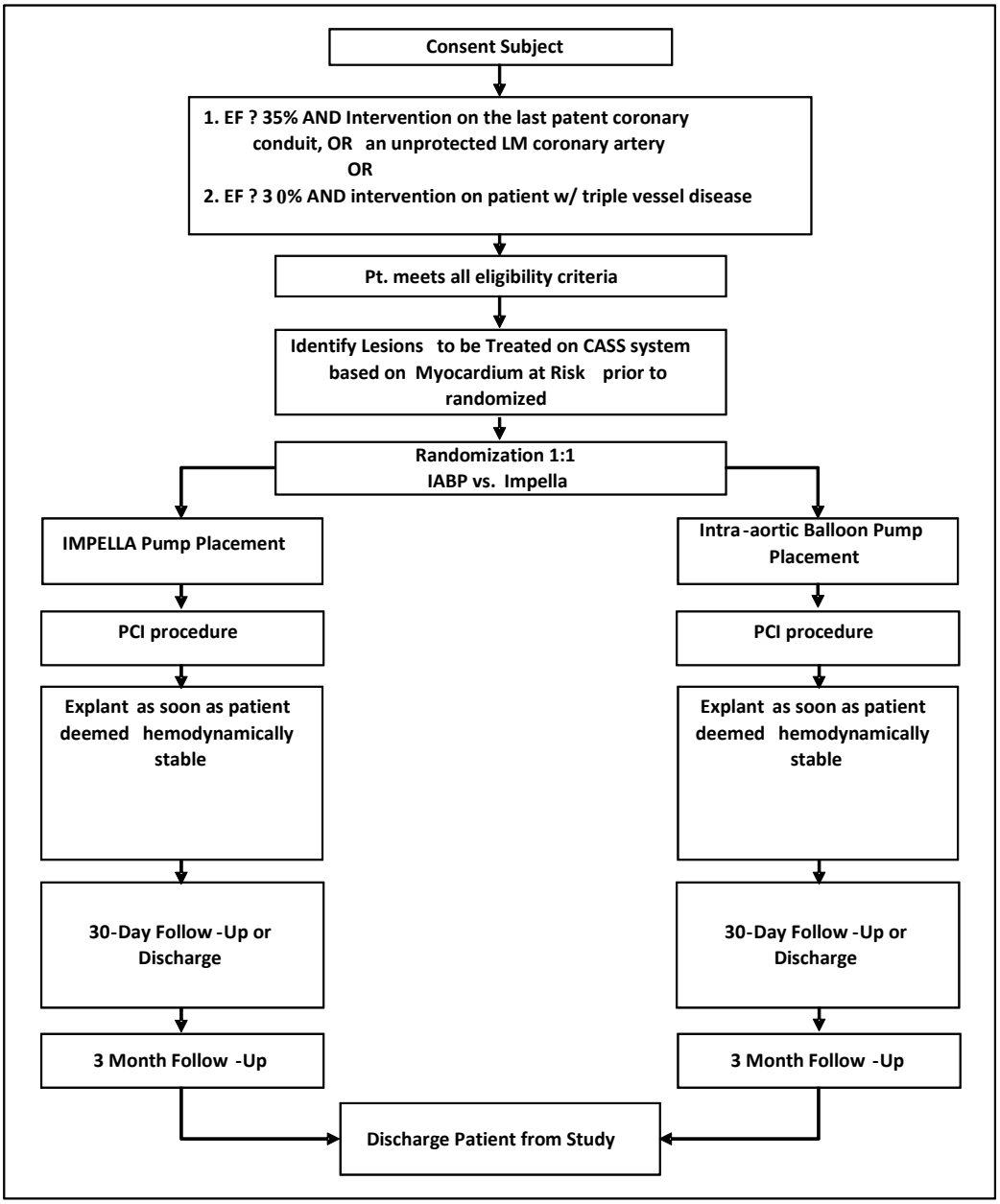
*Exclusion Criteria*

1. ST Myocardial Infarction within 24 hours or CK-MB that have not normalized
2. Pre-procedure cardiac arrest within 24 hours of enrolment requiring CPR
3. Subject is in cardiogenic shock defined as:
   - CI < 2.2 l/min/m2 and PCWP > 15 mmHg
   - Hypotension (systolic BP < 90 mmHg for > 30 minutes or the need for supportive measures to maintain a systolic BP of greater than or equal to 90 mmHg) AND end organ hypoperfusion (cool extremities OR [a urine output of < 30 ml/hour AND a HR > 60 BPM]).
4. Mural thrombus in the left ventricle
5. The presence of a mechanical aortic valve or heart constrictive device
6. Documented presence of aortic stenosis (aortic stenosis graded as $\geq +2$ equivalent to an orifice area of $1.5cm^2$ or less)
7. Documented presence of moderate to severe aortic insufficiency (echocardiographic assessment of aortic insufficiency graded as $\geq +2$)
8. Severe peripheral arterial obstructive disease that would preclude the placement of the IMPELLA® System or IABP device placement
9. Abnormalities of the aorta that would preclude surgery, including aneurysms and extreme tortuosity or calcifications
10. Subject with renal failure (creatinine $\geq$ 4mg/dL)
11. Subject has history of debilitating liver dysfunction with elevation of liver enzymes and bilirubin levels to $\geq$ 3x ULN or Internationalized Normalized Ratio (INR) $\geq$ 2

12. Subject has uncorrectable abnormal coagulation parameters (defined as platelet count ≤75,000/mm3 or INR ≥2.0 or Fibrinogen ≤ 1.50 g/l.)
13. History of recent (within 1 month) stroke or TIA
14. Allergy or intolerance to heparin, aspirin, ADP receptor inhibitors (clopidogrel and ticlid) or contrast media
15. Subject with documented heparin induced thrombocytopenia
16. Participation in the active follow-up phase of another clinical study of an investigational drug or device

The study design is illustrated in Figure 5 below.

Figure 5: PROTECT II study schematic



## B. Accountability of PROTECT II Cohort

A total of 452 subjects were enrolled into the trial: 226 subjects enrolled in the Impella arm and 226 subjects enrolled in the IABP arm. This number represents 69% of the original planned enrollment (654 subjects). The PROTECT II trial was stopped prematurely by the company due to the Data Safety and Monitoring Board (DSMB) recommendation for futility after completing its pre-specified interim analysis at 50% enrollment for each group. More details are below.

Intent-to-Treat Population

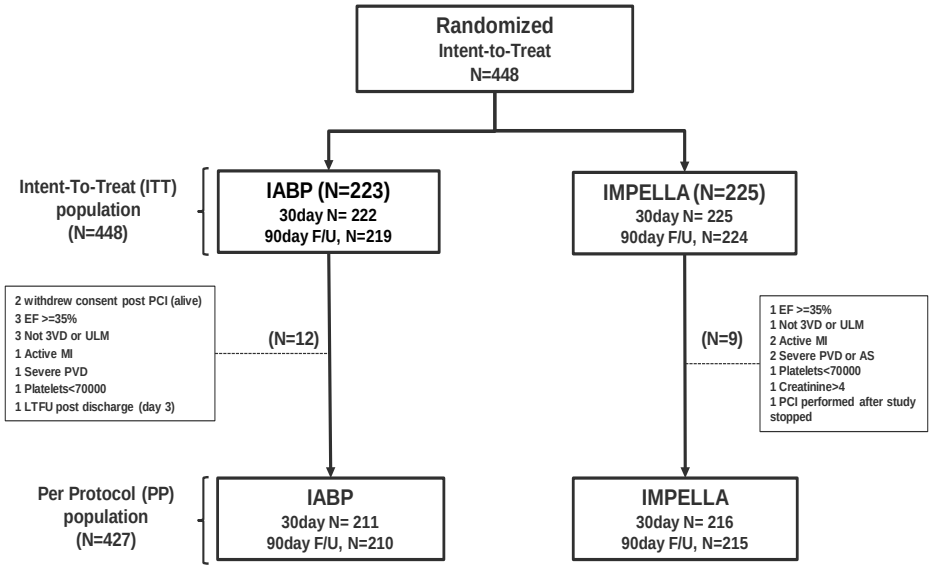
Out of the 452 patients enrolled into the study, three subjects (all in IABP arm) withdrew consent before PCI and device insertion. One patient expired in the Impella arm prior to undergoing PCI treatment and device insertion. Thus, the primary analysis includes 448 Intent-to-Treat (ITT) patients randomized to either the Impella 2.5 System (n=225) or IABP (n=223), regardless of whether or not they received the device and the duration of follow-up.

Per-Protocol Analysis Population

Prior to accessing the data, the monitoring of the patient eligibility criteria by HCRI identified a total of twenty-one (21) subjects who did not meet the study inclusion or exclusion criteria. These cases were to be excluded from the ITT. The remainder formed the Per-Protocol (PP) population. Nine of the subjects excluded from the ITT population were in the Impella arm and twelve subjects excluded from the ITT population were in the IABP arm. The PP analysis population consists then of 427 subjects, of which 216 subjects were randomized to the Impella arm and 211 subjects were randomized to the IABP arm.

The study flow is represented in Figure 6 below, showing the ITT and PP populations and the sample sizes of each population at 30 day and 90 day follow-up.

Figure 6: Study Flow Schematic



### C. Limitations of Interpretation of Study Results

Fifty percent (50%) enrollment was achieved on February 26, 2010 with the enrollment of the 327$^{th}$ subject. This subject completed the study (3 month visit) on May 27, 2010. Approximately 7 months later, HCRI completed the study activities necessary to lock the database for the interim analysis and prepare an interim analysis report for the DSMB. In these 7 months of intervening time, 125 additional subjects were enrolled into the study. The results from the additional patients were excluded from the interim analysis.

The DSMB met on November 22, 2010 and recommended that the trial be halted due to a futility determination based on the pre-specified primary endpoint (composite MAE at 30 days), which was calculated on the first 327 patients enrolled in the study. The DSMB also expressed concern regarding safety trends identified in 3 of the pre-specified patient cohorts:

1) patients receiving rotational atherectomy;
2) patients undergoing PCI on an unprotected left main/last patent conduit; and
3) patients judged to be in the highest risk based on STS score.

ABIOMED made the decision to stop the trial due to the futility determination mentioned above on December 2, 2010 and notified the FDA and the investigators.

The study was formally ended on December 6, 2010, at which time the data were then unlocked.

### D. Study Population Demographics and Baseline Characteristics

Patient baseline characteristics for all enrolled patients (ITT N=448, 69% of planned cohort) are summarized in Table 9 below. Overall, patients had depressed ventricular function, multi-vessel disease (76% of patients), unprotected left main disease (24% of patients), and at least one of the following additional risk factors: advanced age, female, diabetes, peripheral vascular disease, history of angina, heart failure or complex lesion anatomy (type B or C lesions).

Two thirds of the patients were deemed inoperable. Subjects presented with an average LVEF of 24%±6%, a Syntax score of 30±13, an STS mortality score of 6%±6% and an STS combined mortality and morbidity score of 30%±15%. Only one third of this population had received implantable defibrillators despite the low LVEF.
Of note, Impella patients presented more frequently with chronic heart failure (91.1% vs. 83.4%, p=0.014) and had more often prior CABG (38.2% vs. 28.7%, p=0.033) compared to IABP patients, respectively.

Table 9: Patient Baseline Characteristics (ITT population)

| | All Patients (n=448) | Impella Patients (n=225) | IABP Patients (n=223) |
|---|---|---|---|
| **Age**<br>Mean±SD (N)<br>Range (Min,Max) | 67.3±10.8 (448)<br>(37,90) | 67.7±10.8 (225)<br>(40,90) | 67.0±10.7 (223)<br>(37,90) |
| **Gender** - Male | 80.4% (360/448) | 79.6% (179/225) | 81.2% (181/223) |
| **Ethnicity and Race** | | | |
| Hispanic/Latino | 7.6% (34/448) | 8.4% (19/225) | 6.7% (15/223) |
| American Indian | 0.4% (2/448) | 0.9% (2/225) | 0.0% (0/223) |
| Asian | 2.7% (12/448) | 1.3% (3/225) | 4.0% (9/223) |
| African American | 13.4% (60/448) | 10.7% (24/225) | 16.1% (36/223) |
| Hawaiian; Pacific Islander | 0.7% (3/448) | 0.4% (1/225) | 0.9% (2/223) |
| Caucasian | 78.8% (353/448) | 83.1% (187/225) | 74.4% (166/223) |
| Other | 4.0% (18/448) | 3.6% (8/225) | 4.5% (10/223) |
| **Weight** (lbs)<br>Mean±SD (N)<br>Range (Min,Max) | 183.8±44.1 (448)<br>(99.0,417.0) | 183.2±41.3 (225)<br>(100.0,320.0) | 184.3±46.7 (223)<br>(99.0,417.0) |
| **Height** (in)<br>Mean±SD (N)<br>Range (Min,Max) | 67.7±3.7 (448)<br>(58.0,78.0) | 67.8±3.7 (225)<br>(59.0,76.2) | 67.6±3.7 (223)<br>(58.0,78.0) |
| **Cardiac History** | | | |
| CAD in a first degree relative | 58.7% (237/404) | 59.5% (119/200) | 57.8% (118/204) |
| Prior Myocardial Infarction | 67.6% (302/447) | 69.2% (155/224) | 65.9% (147/223) |
| History of Angina | 66.3% (295/445) | 69.5% (155/223) | 63.1% (140/222) |
| CHF | 87.3% (391/448) | 91.1% (205/225) | 83.4% (186/223) |
| NYHA Class III or IV | 66.1% (222/336) | 67.4% (120/178) | 64.6% (102/158) |
| Pacemaker/AICD | 32.9% (147/447) | 34.7% (78/225) | 31.1% (69/222) |
| Cardiomyopathy | 69.2% (310/448) | 69.3% (156/225) | 69.1% (154/223) |
| Arrhythmia | 48.9% (218/446) | 50.9% (114/224) | 46.8% (104/222) |
| **Prior Cardiac Procedures** | | | |
| Thrombolytic Therapy | 5.7% (25/442) | 4.9% (11/223) | 6.4% (14/219) |
| PCI | 39.2% (175/446) | 41.5% (93/224) | 36.9% (82/222) |
| CABG | 33.5% (150/448) | 38.2% (86/225) | 28.7% (64/223) |
| Valve Surgery | 3.3% (15/448) | 3.1% (7/225) | 3.6% (8/223) |
| Other Cardiac Surgery | 7.2% (32/446) | 6.3% (14/224) | 8.1% (18/222) |
| Other Cardiac Intervention | 14.8% (66/446) | 14.3% (32/224) | 15.3% (34/222) |
| **CABG Evaluation:**<br>Subject was evaluated for CABG as treatment | 64.1% (287/448) | 63.6% (143/225) | 64.6% (144/223) |
| **The reason for not performing a CABG:** | | | |
| Subject refused surgery | 19.2% (55/287) | 22.4% (32/143) | 16.0% (23/144) |

| | All Patients (n=448) | Impella Patients (n=225) | IABP Patients (n=223) |
|---|---|---|---|
| Subject not a candidate for CABG based on medical condition | 80.8% (232/287) | 77.6% (111/143) | 84.0% (121/144) |
| **Other Medical History** | | | |
| Peripheral Vascular Disease | 26.1% (116/445) | 25.7% (57/222) | 26.5% (59/223) |
| Prior Stroke | 14.7% (66/448) | 12.9% (29/225) | 16.6% (37/223) |
| Diabetes Mellitus | 51.3% (230/448) | 52.0% (117/225) | 50.7% (113/223) |
| Hypertension | 86.4% (387/448) | 87.6% (197/225) | 85.2% (190/223) |
| COPD | 27.6% (123/445) | 25.9% (58/224) | 29.4% (65/221) |
| Renal Insufficiency | 26.6% (119/447) | 23.1% (52/225) | 30.2% (67/222) |
| History of Tobacco Use | 69.6% (307/441) | 71.5% (158/221) | 67.7% (149/220) |
| **LVEF** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 23.79±6.32 (445)<br>(10.00,35.00) | 23.45±6.31 (224)<br>(10.00,35.00) | 24.14±6.33 (221)<br>(10.00,35.00) |
| **Syntax Score Pre-PCI** | | | |
| Mean±SD (N)<br>Range (Min,Max)<br>Median (IQ Range) | 30.32±13.13 (144)<br>(5.00,68.50)<br>30.50 (19.75 - 38.25) | 29.31±13.50 (157)<br>(3.00,85.50)<br>28.00 (19.00 - 36.50) | 29.79±13.31 (301)<br>(3.00,85.50)<br>29.00 (19.50 - 37.50) |
| **STS Mortality Score** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 5.93±6.48 (448)<br>(0.40,60.00) | 5.86±5.98 (225)<br>(0.40,41.20) | 6.01±6.97 (223)<br>(0.40,60.00) |
| **STS Mortality and Morbidity Score** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 29.52±15.34 (448)<br>(1.60,74.70) | 28.80±14.97 (225)<br>(1.60,74.50) | 30.24±15.71 (223)<br>(6.90,74.70) |
| **Logistic EuroScore** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 18.39±17.44 (448)<br>(0.82,94.53) | 18.76±17.41 (225)<br>(0.82,94.53) | 18.03±17.49 (223)<br>(1.33,91.15) |

**Procedural Characteristics**

In both study arms, more lesions were attempted than originally anticipated, as 27% of all patients had a lesion treated that was not identified as a target lesion in the pre-PCI revascularization treatment plan. The number of attempted lesions and deployed stents were similar between the two groups (Table 10).

Differences were observed between the two study arms with respect to the use of adjunctive therapies. In the Impella 2.5 System arm, glycoprotein IIb/IIIa receptor antagonists were used less frequently, in 13.8% of Impella patients vs. 26% of IABP patients. Rotational atherectomy was used more frequently in Impella patients (14%) vs. IABP patients (9%). The use of rotational atherectomy was also more vigorous in the Impella arm with more runs per patient, more passes per lesion, longer treatment durations and more frequently performed in unprotected left main lesions. More stents were deployed in the Impella arms compared to the IABP in patients that had atherectomy. Finally, the volume of contrast used was significantly greater in the Impella 2.5 System arm. Patients randomized to IABP had longer duration of support compared with those on Impella 2.5 System (8.4 hours vs. 1.9 hours). Instructions in the protocol called for device support to be discontinued after the PCI procedure if the patient was determined to be hemodynamically stable. In total, 36.7% of patients in the IABP arm required additional support post-PCI and were discharged from the catheterization laboratory (Cath Lab) on IABP support compared to 5.9% of patients in the Impella arm, who were discharged from the Cath Lab on Impella support.

Table 10: Procedural characteristics

| Procedural Characteristic | All Patients (n=448) | Impella Patients (n=225) | IABP Patients (n=223) |
|---|---|---|---|
| **Lesion and Rotational Atherectomy Characteristic** | | | |
| **Number of lesions treated** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 2.88±1.48 (448)<br>(1.00,8.00) | 2.86±1.43 (225)<br>(1.00,8.00) | 2.90±1.53 (223)<br>(1.00,8.00) |
| **% Patients with at least one lesion treated that was not a target lesion for the** | | | |
| Percent | 26.7%<br>(119/446) | 27.7%<br>(62/224) | 25.7%<br>(57/222) |
| **Number of stents placed** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 3.01±1.83 (444)<br>(0.00,12.00) | 3.07±1.77 (222)<br>(0.00,10.00) | 2.94±1.90 (222)<br>(0.00,12.00) |
| **Total of longest duration of coronary balloon inflation (second)** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 58.23±93.67 (399)<br>(0.00,1500.00) | 63.86±125.69 (200)<br>(0.00,1500.00) | 52.58±41.17 (199)<br>(0.00,252.00) |
| **% Patients with chronic total occlusion (CTO) lesions treated** | | | |
| Percent | 9.6%<br>(43/448) | 9.3%<br>(21/225) | 9.9%<br>(22/223) |
| **Use of atherectomy rotablation during index procedure** | | | |

| Procedural Characteristic | All Patients (n=448) | Impella Patients (n=225) | IABP Patients (n=223) |
|---|---|---|---|
| Percent | 11.6% (52/448) | 14.2% (32/225) | 9.0% (20/223) |
| **Total number of passes when atherectomy was used** | | | |
| Median (IQ Range) | 4.00 (2.00 - 8.00) | 5.00 (3.50 - 9.50) | 2.00 (2.00 - 4.00) |
| **Average number of passes per lesion when atherectomy was used** | | | |
| Median (IQ Range) | 2 (1 - 4) | 3 (2 - 5) | 1 (1 - 2) |
| **Average duration/run time per lesion when atherectomy was used (second)** | | | |
| Median (IQ Range) | 47.50 (32.50 - 85.00) | 60.00 (40.00 - 118.00) | 40.00 (20.00 - 47.00) |
| **Average number of stent placed when atherectomy was used** | | | |
| Mean±SD (N) | | 3.44±1.61 (32) (1.00 – 8.0) | 2.50±1.40 (20) (0.0 – 6.0) |
| **Procedural Characteristics** | | | |
| **Volume for contrast administered during the index procedure (c.c.)** | | | |
| Mean±SD (N) Range (Min,Max) | 253.86±129.26 (443) (40.00,970.00) | 266.73±141.80 (222) (40.00,970.00) | 240.94±114.17 (221) (50.00,700.00) |
| **Duration of device support (hour)** | | | |
| Mean±SD (N) Range (Min,Max) | 5.12±15.81 (439) (0.20,199.32) | 1.87±2.69 (221) (0.28,26.38) | 8.41±21.81 (218) (0.20,199.32) |
| **Device support continued more than 3 hours post index procedure** | | | |
| Percent | 16.6% (73/440) | 4.5% (10/221) | 28.8% (63/219) |
| **Patients discharged from Cath Lab on device support** | | | |
| Percent | 21.2% (93/438) | 5.9% (13/220) | 36.7% (80/218) |
| **IV Fluid Volume subject received during procedure (cc)** | | | |
| Mean±SD (N) Range (Min,Max) | 486.10±518.26 (338) (0,5000) | 555.65±623.07 (168) (0,5000) | 417.38±377.38 (170) (0,2250) |
| **Heparin administered during procedure** | | | |
| Percent | 88.4% (395/447) | 93.3% (210/225) | 83.3% (185/222) |
| **IIb/IIIa Inhibitors used at baseline** | | | |
| Percent | 19.9% (89/448) | 13.8% (31/225) | 26.0% (58/223) |
| **Periprocedural transfusion required** | | | |

| Procedural Characteristic | All Patients (n=448) | Impella Patients (n=225) | IABP Patients (n=223) |
|---|---|---|---|
| Percent | 2.7% (12/447) | 3.6% (8/224) | 1.8% (4/223) |
| **Number of units transfused during the procedure or at pump removal combined** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 2.42±1.44 (12)<br>(1.00,5.00) | 2.25±1.49 (8)<br>(1.00,5.00) | 2.75±1.50 (4)<br>(2.00,5.00) |
| **Impella Pump flow during procedure (L/min)** | | | |
| Mean±SD (N)<br>Range (Min,Max) | 1.90±0.27 (217)<br>(1.10,2.50) | 1.90±0.27 (217)<br>(1.10,2.50) | N/A |

### E. Safety and Effectiveness Results

As discussed above, the pre-specified primary endpoint for the PROTECT II study was a 30-day composite MAE rate (10 components)., where the study hypothesis was to demonstrate that prophylactic use of Impella 2.5 System was superior to IABP in preventing intra- and post-procedural MAEs in this patient population. A pre-specified interim look by the Data Safety Monitoring Board (DSMB) at 50% enrollment (327 patients) concluded in a recommendation for early discontinuation of the study for futility as the "*Board found no statistically significant differences in major adverse events*" between the Impella and IABP arms, with some identified safety concerns as well.

Abiomed formally terminated the study on December 6, 2010, at which point they unlocked all of the data (n=452) and performed additional analyses on the total cohort of patients enrolled into the PROTECT II study and available for analysis (n=448; 225 Impella subjects and 223 IABP subjects). These analyses concluded the following:

1. There was an imbalance between the two groups in the use of rotational atherectomy - more frequent and more vigorous in the Impella arm as compared to IABP.
2. The analysis of the data available for the 448 patient cohort (69% of planned enrollment) did not appear consistent with the futility statements made by the DSMB which were based on a review of 327 patients (50% enrollment).
3. Some of the negative trends in outcomes for the Impella arm observed at interim appear to be attenuated when the totality of the data was reviewed.
4. Contrary to the interim assumption, the analysis that includes the full patient cohort suggests that Impella 2.5 System outcomes improved over the course of the trial (i.e., from 30-day follow-up to 90-day follow-up), while the outcomes for the IABP arm appear to remain about the same between the two follow-up periods.

These findings, in addition to the possibility that a learning curve was present and may have skewed the results of early interventions, led FDA to consider the possibility that the treatment effect may simply not have been realized in this terminated study. As such, the FDA review of PMA P140003 included the totality of all data available (descriptive only) for the Impella 2.5 System (when used in HRPCI patients) in its evaluation of the

safety and effectiveness of the Impella 2.5 System when used as intended. The primary data set utilized for this evaluation came from the 452 patients enrolled into the PROTECT II study (30-day and 90-day data), as well as supporting/supplemental evidence from the literature and data from the USpella Registry.

The 10 component composite MAE rate (summarized in Table 11a and 11b) showed a numerical difference at 30 days in both the ITT and PP populations at 69% of the planned enrollment in favor of Impella. The numerical difference in MAE rates between the two groups increases at 90 days for the PP population (the longest study follow-up).

Intent-to-Treat Population

At 69% of the planned enrollment, the 30 day MAE rate was 35.1% in the Impella arm compared to 40.1% in the IABP arm (Table 11a and Figure 7a). The 90 day MAE rate showed trends in favor of Impella, (40.6% vs. 49.3%, Table 11a, see Figure 7a).

Per Protocol Population

At 69% enrollment, 30 day MAE rate was 34.3% in the Impella arm compared to 42.2% in the IABP arm. Compared with IABP, the 90 day MAE rate was lower in the Impella arm (40.0% vs. 51.0%) yielding a relative risk reduction of 22% (Table 11b, Figure 7b).

Table 11a: Composite MAE at 30 days and 90 days (Intent-to-Treat Population)

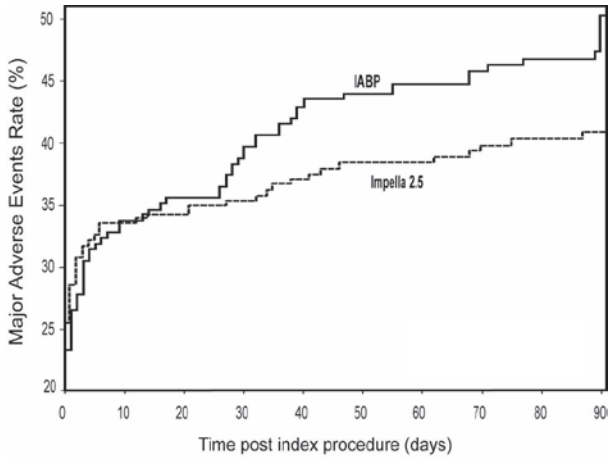
| **Composite MAE (ITT Population)** | **Impella Patients** | **IABP Patients** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 35.1% (79/225) | 40.1% (89/222) | -5.0% | -12.5% |
| 90 Day Follow-up | 40.6% (91/224) | 49.3% (108/219) | -8.7% | -17.6% |

Table 11b: Composite MAE at 30 days and 90 days (Per-Protocol Population)

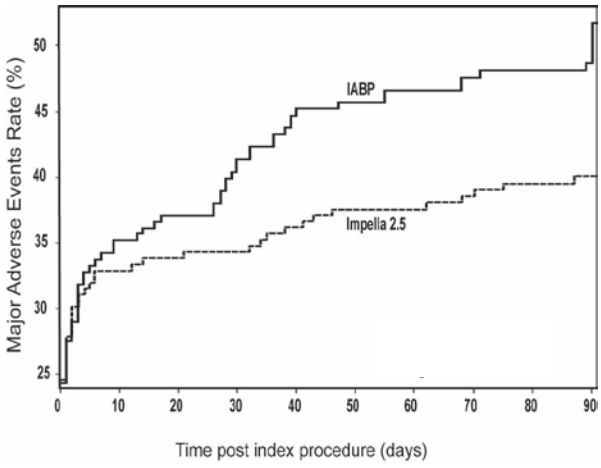
| **Composite MAE (PP Population)** | **Impella Patients** | **IABP Patients** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 34.3% (74/216) | 42.2% (89/211) | -7.9% | -18.7% |
| 90 Day Follow-up | 40.0% (86/215) | 51.0% (107/210) | -11.0% | -21.6% |

Figure 7: Kaplan-Meier curves for major adverse events

a. Intent-to-Treat Population




b. Per-Protocol Population




| ITT | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 225 | 168 | 145 | 120 |
| IABP Patients At Risk | 223 | 171 | 133 | 107 |

| PP | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 216 | 163 | 141 | 116 |
| IABP Patients At Risk | 211 | 160 | 124 | 99 |

Pre-specified Subgroup Analyses on the Primary Endpoint

*Learning curve*

The results of the pre-specified analysis without the Impella roll-in subject suggested the presence of a learning curve in the trial. Patients in the Impella arm, with the first subject excluded, had fewer MAEs at 30 days compared to the 30 day rate that was observed for all Impella patients (Tables 11a and 11b). This had the effect of enlarging the observed differences in MAE rates at 30 and 90 days when comparing the adjusted Impella cohort to IABP (Tables 12a and 12b).

Table 12a: Subgroup without Impella roll-in subject (Intent-to-Treat Population)

| **Subgroup Analysis – Without Impella Roll-In Subject (ITT)** | **Impella Patients (n=167)** | **IABP Patients (n=223)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 31.7% | 40.1% | -8.4% | -20.9% |
| 90 Day Follow-up | 38.0% | 49.3% | -11.3% | -22.9% |

Table 12b: Subgroup without Impella roll-in subject (Per-Protocol Population)

| **Subgroup Analysis – Without Impella Roll-In Subject (PP)** | **Impella Patients (n=162)** | **IABP Patients (n=211)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 32.1% | 42.2% | -10.1% | -23.9% |
| 90 Day Follow-up | 38.5% | 51.0% | -12.5% | -24.5% |

*Atherectomy/Non-atherectomy*

Atherectomy was not used as a part of the PCI procedure in 88% of the enrolled patients. In this subgroup, a relative reduction of MAE risk for ITT patients at 30 days favoring the Impella 2.5 System was similar in magnitude to the reduction observed when the first Impella patient was removed was observed at 30 days. Relative reductions in the MAE rate for PP treated patients were observed at 30 and 90 days (Table 13a and 13b).

Table 13a: Subgroup without Rotational Atherectomy (Intent-to-Treat Population)

| **Subgroup Analysis – No Rotational Atherectomy (ITT)** | **Impella Patients (n=193)** | **IABP Patients (n=203)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 30.6% | 39.6% | -9.0% | -22.7% |
| 90 Day Follow-up | 38.5% | 48.7% | -10.2% | -20.9% |

Table 13b: Subgroup without Rotational Atherectomy (Per-Protocol Population)

| **Subgroup Analysis – No Rotational Atherectomy (PP)** | **Impella Patients (n=184)** | **IABP Patients (n=191)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 29.3% | 41.9% | -12.6% | -30.1% |
| 90 Day Follow-up | 35.5% | 50.5% | -15.0% | -29.7% |

An analysis of the composite MAE for the subjects treated with rotational atherectomy is summarized in Tables 14a (ITT Population) and 14b (PP Population). This was a small subgroup consisting of 32 Impella subjects and 20 IABP subjects in the ITT and PP groups. There was a numerically higher observed rate of MAE in Impella subjects compared to IABP treated with rotational atherectomy for both the ITT and PP populations.

Table 14a: Subgroup with Rotational Atherectomy (Intent-to-Treat Population)

| **Subgroup Analysis – With Rotational Atherectomy (ITT)** | **Impella Patients (n=32)** | **IABP Patients (n=20)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 62.5% | 45.0% | +17.5% | +38.9% |
| 90 Day Follow-up | 65.6% | 55.0% | +10.6% | +19.3% |

Table 14b: Subgroup with Rotational Atherectomy (Per-Protocol Population)

| Subgroup Analysis – With Rotational Atherectomy (PP) | Impella Patients (n=32) | IABP Patients (n=20) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 62.5% | 45.0% | +17.5% | +38.9% |
| 90 Day Follow-up | 65.6% | 55.0% | +10.6% | +19.3% |

*Angioplasty Indication*
An analysis of the composite MAE for the subgroup whose indication for angioplasty was unprotected left main or last patent coronary conduit (24% of the entire PROTECT II cohort) is summarized in Tables 15a and 15b (ITT and PP Populations respectively).

The composite MAE rate was similar between the study arms at 30 days in the ITT group (41.5% for Impella vs. 40.7% for IABP). There were numerically fewer MAEs in the Impella arm compared to the IABP arm in the ITT population (44.2% vs. 50.0%) and PP population (41.7% vs. 50.9%) at 90 days.

Table 15a: Subgroup of Unprotected Left Main/Last Patent Conduit (Intent-to-Treat Population)

| Subgroup Analysis – Unprotected Left Main (ITT) | Impella Patients (n=53) | IABP Patients (n=54) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 41.5% | 40.7% | +0.8% | +2.0% |
| 90 Day Follow-up | 44.2% | 50.0% | -5.8% | -11.6% |

Table 15b: Subgroup of Unprotected Left Main/Last Patent Conduit (Per-Protocol Population)

| Subgroup Analysis – Unprotected Left Main (PP) | Impella Patients (n=49) | IABP Patients (n=53) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 38.8% | 41.5% | -2.7% | -6.5% |
| 90 Day Follow-up | 41.7% | 50.9% | -9.2% | -18.1% |

An analysis of the composite MAE for the subgroup whose indication for angioplasty was three-vessel disease is summarized in Tables 16a (ITT Population) and 16b (PP Population). The observed composite MAE rate was numerically lower for Impella vs. IABP at 30 and 90 days in the ITT group. In the Per-Protocol population, a trend in favor of Impella was observed at 90 days (39.5% MAE for Impella vs. 51.0% MAE for IABP).

Table 16a: Subgroup of Three Vessel Disease (Intent-to-Treat Population)

| Subgroup Analysis – Three Vessel Disease (ITT) | Impella Patients (n=169) | IABP Patients (n=172) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 33.1% | 39.9% | -6.8% | -17.0% |
| 90 Day Follow-up | 39.5% | 49.1% | -9.6% | -19.6% |

Table 16b: Subgroup of Subgroup of Three Vessel Disease (Per-Protocol Population)

| Subgroup Analysis – Three Vessel Disease (PP) | Impella Patients (n=158) | IABP Patients (n=167) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 32.9% | 42.4% | -9.5% | -22.4% |
| 90 Day Follow-up | 39.5% | 51.0% | -11.5% | -22.5% |

*Outcomes as a function of morbidity: STS mortality score*

An analysis of the composite MAE for the subgroup with STS mortality scores < 10 is summarized in Tables 17a (ITT Population) and 17b (PP Population). The composite MAE rate in the ITT group is numerically lower for Impella vs. IABP at 30 days (33.2% for Impella vs. 38.7% for IABP) and at 90 days (37.4% for Impella vs. 48.6% for IABP). In the PP population, there was a numerical trend favoring Impella at 90 days (36.1% MAE for Impella vs. 50.6% MAE for IABP).

Table 17a: Subgroup of STS Mortality Score < 10 (Intent-to-Treat Population)

| Subgroup Analysis – STS Mortality Score < 10 (ITT) | Impella Patients (n=187) | IABP Patients (n=187) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 33.2% | 38.7% | -5.5% | -14.2% |
| 90 Day Follow-up | 37.4% | 48.6% | -11.2% | -23.0% |

Table 17b: Subgroup of STS Mortality Score < 10 (Per-Protocol Population)

| Subgroup Analysis – STS Mortality Score < 10 (PP) | Impella Patients (n=180) | IABP Patients (n=175) | Difference | Relative reduction or increase |
|---|---|---|---|---|
| 30 days or Discharge | 31.7% | 41.1% | -9.4% | -22.9% |
| 90 Day Follow-up | 36.1% | 50.6% | -14.5% | -28.7% |

An analysis of the composite MAE for the subgroup with STS mortality scores ≥ 10 is summarized in Tables 18a (ITT Population) and 18b (PP Population). This subgroup represents the highest risk patients enrolled in the trial. The composite MAE rate is

similar for Impella vs. IABP at 30 days in the ITT group (44.7% for Impella vs. 47.2% for IABP) and the PP population (47.2% for Impella vs. 47.2% for IABP). The rates remain similar between the two arms at 90 days for both the ITT (56.8% for Impella vs. 52.8% for IABP), and PP populations (60.0% for Impella vs. 52.8% for IABP).

Table 18a: Subgroup of STS Mortality Score ≥ 10 (Intent-to-Treat Population)

| **Subgroup Analysis – STS Mortality Score ≥ 10 (ITT)** | **Impella Patients (n=38)** | **IABP Patients (n=36)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 44.7% | 47.2% | -2.5% | -5.3% |
| 90 Day Follow-up | 56.8% | 52.8% | +4.0% | +7.6% |

Table 18b: Subgroup of STS Mortality Score ≥ 10 (Per-Protocol Population)

| **Subgroup Analysis – STS Mortality Score ≥ 10 (PP)** | **Impella Patients (n=36)** | **IABP Patients (n=36)** | **Difference** | **Relative reduction or increase** |
|---|---|---|---|---|
| 30 days or Discharge | 47.2% | 47.2% | 0% | 0% |
| 90 Day Follow-up | 60.0% | 52.8% | +7.2% | +13.6% |

The above results show that: 1) patients supported with Impella tend to have a lower composite MAE rate than those supported with IABP in most of the subgroups; 2) there appears to be a learning curve associated with the use of the device that can be seen when removing from the analysis the first Impella subject at each site, and 3) the use of atherectomy appears to be potentially a confounding variable that may have affected the results of the trial (including the high STS group patient subgroup).

**Secondary Safety Results**

The ten major adverse events components of the primary endpoint were analyzed separately, in both a non-hierarchical and hierarchical manner. Tables 19a and 19b below summarize the individual major adverse events components in a non-hierarchical manner, in which all the MAEs for all the subjects are represented in the components. Table 19a gives the results for the MAE components for the Intent-to-Treat population to 30 days or discharge, whichever is longer, and at 90 days. None of the differences between the IABP and Impella study arms for the individual MAE components were numerically different at any time point for the ITT with the exception of repeat revascularization at 90 days, where i26 IABP subjects vs. 14 Impella subjects required repeat revascularization.

Table 19b summarizes the results for the MAE components for the Per-Protocol population to 30 days or discharge whichever was longer, and at 90 days. None of the numerical differences between the study arms for the individual MAE components were significant at any time point with the exception of repeat revascularization at 90 days, where 26 IABP subjects vs. 13 Impella subjects required repeat revascularization.

Table 19a: Individual MAE Components (ITT Population) Non-hierarchical

| MAE to 30 Days or Discharge | 30 Days | | 90 Days | |
|---|---|---|---|---|
| | Impella Patients (n=225) | IABP Patients (n=222) | Impella Patients (n=224) | IABP Patients (n=219) |
| Death | 7.6% (17/225) | 5.9% (13/222) | 12.1% (27/224) | 8.7% (19/219) |
| Stroke/TIA | 0.4% (1/225) | 1.8% (4/222) | 1.3% (3/224) | 2.7% (6/219) |
| Myocardial Infarction | 17.8% (40/225) | 12.2% (27/222) | 18.8% (42/224) | 16.0% (35/219) |
| Repeat Revascularization | 3.6% (8/225) | 5.9% (13/222) | 6.3% (14/224) | 11.9% (26/219) |
| Need for Cardiac or Vascular Operation or Limb ischemia | 1.8% (4/225) | 2.3% (5/222) | 2.2% (5/224) | 3.7% (8/219) |
| Acute Renal Dysfunction | 7.1% (16/225) | 7.7% (17/222) | 9.4% (21/224) | 11.0% (24/219) |
| CPR or Ventricular Arrhythmia requiring Cardioversion | 10.2% (23/225) | 7.2% (16/222) | 12.5% (28/224) | 10.0% (22/219) |
| Increase in Aortic Insufficiency | 0.0% (0/225) | 0.0% (0/222) | 0.0% (0/224) | 0.0% (0/219) |
| Severe Hypotension | 10.7% (24/225) | 11.7% (26/222) | 10.7% (24/224) | 11.9% (26/219) |
| Angiographic Failure | 3.6% (8/225) | 1.8% (4/222) | 3.6% (8/224) | 1.8% (4/219) |

Table 19b: Individual MAE Components to 30 Days or Discharge (PP Population) - Non hierarchical

| MAE to 30 Days or Discharge | 30 Days | | 90 Days | |
|---|---|---|---|---|
| | Impella Patients (n=216) | IABP Patients (n=211) | Impella Patients (n=215) | IABP Patients (n=210) |
| Death | 6.9% (15/216) | 6.2% (13/211) | 11.6% (25/215) | 9.0% (19/210) |
| Stroke/TIA | 0.5% (1/216) | 1.9% (4/211) | 1.4% (3/215) | 2.4% (5/210) |
| Myocardial Infarction | 17.1% (37/216) | 12.8% (27/211) | 18.1% (39/215) | 16.7% (35/210) |
| Repeat Revascularization | 3.2% (7/216) | 6.2% (13/211) | 6.0% (13/215) | 12.4% (26/210) |
| Need for Cardiac or Vascular Operation or Limb ischemia | 1.9% (4/216) | 2.4% (5/211) | 2.3% (5/215) | 3.8% (8/210) |

| MAE to 30 Days or Discharge | 30 Days | | 90 Days | |
|---|---|---|---|---|
| | Impella Patients (n=216) | IABP Patients (n=211) | Impella Patients (n=215) | IABP Patients (n=210) |
| Acute Renal Dysfunction | 7.4% (16/216) | 8.1% (17/211) | 9.8% (21/215) | 11.4% (24/210) |
| CPR or Ventricular Arrhythmia requiring Cardioversion | 9.7% (21/216) | 7.6% (16/211) | 12.1% (26/215) | 10.5% (22/210) |
| Increase in Aortic Insufficiency | 0.0% (0/216) | 0.0% (0/211) | 0.0% (0/215) | 0.0% (0/210) |
| Severe Hypotension | 10.2% (22/216) | 12.3% (26/211) | 10.2% (22/215) | 12.4% (26/210) |
| Angiographic Failure | 3.7% (8/216) | 1.9% (4/211) | 3.7% (8/215) | 1.9% (4/210) |

**Secondary Effectiveness Results**

Cardiac Power Output (CPO)

When measured by maximal drop in CPO from baseline, Impella appeared to provide better hemodynamic support compared to IABP (-0.04±0.24 vs. -0.14±0.27 Watts, respectively).

Creatinine Clearance

The mean change in creatinine clearance from baseline to 24 hours post-procedure was equivalent for the two study arms: 4.64 ± 15.06 ml/min for the Impella arm and 4.66 ± 13.55 ml/min for the IABP arm.

Impella Pump Output

A secondary effectiveness endpoint was defined as the failure of the Impella 2.5 System to maintain a pump output of > 1.0 L/min for more than five minutes while at a performance level P5 or higher in the Impella patients during the procedure. Analysis of the data of flow vs. P-level for Impella subjects showed no failures (0%). In all cases the Impella 2.5 System, when set at performance level P5 or higher, maintained flows above 1.0 L/min.

IABP Pressure Augmentation

A secondary effectiveness endpoint was the failure of the IABP to augment diastolic pressure above the peak systolic pressure for more than five minutes in the IABP patients. This endpoint was unable to be measured for the study, as the data analysis required access to IABP console data, which was not possible without the IABP manufacturer's approval. Alternative sources of data (i.e. analysis of IABP device failures and the MAE rate for hypotension for the IABP arm) do not suggest that there would have been significant failures of the IABP to augment diastolic pressure above the peak systolic pressure for more than five minutes in the IABP patients.

### F. Financial Disclosure

The pivotal clinical study included 112 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

### A. Further PROTECT II Analysis

An additional *post hoc* analysis was conducted on the primary endpoint of the PROTECT II data set and provided additional clinical information.

This analysis used a different, prognostically relevant definition of peri-procedural myocardial infarction. Specifically, the 2007 universal definition of MI used in the trial has since changed to reflect current knowledge. The additional analysis incorporated the identical data from PROTECT II but was conducted using an 8x Upper Limit of Normal (ULN) threshold for cardiac biomarker release to define peri-procedural MI in order to reflect a contemporary and prognostically relevant definition of MI.

At 90 days, lower MAE (same 10 components as defined in the PROTECT II Study) and major adverse cardiac and cerebrovascular events (MACCE - a subset of the components used in the MAE definition) rates were observed in the Impella group compared to IABP when this contemporary definition of peri-procedural myocardial infarction (8x ULN) was used. (Tables 20a and 20b).

Table 20a: Composite MAE at 30 and 90 Days using contemporary definition for peri-procedural MI (8x ULN) (Intent-to-Treat Population and Per-Protocol Population)

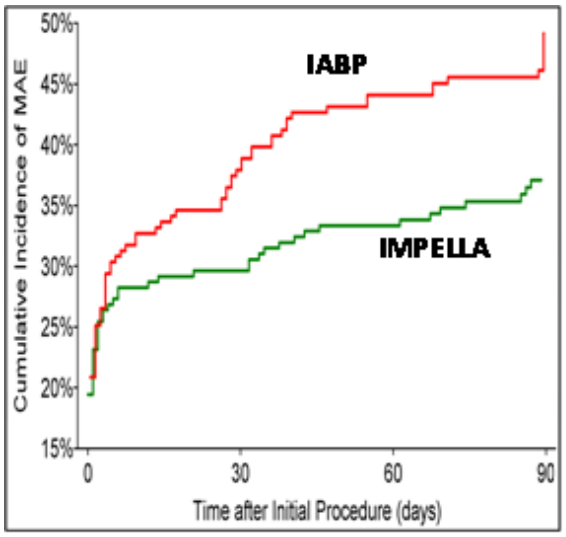
| MAE at 30 Days | Impella | IABP | Difference | Relative reduction or increase |
|---|---|---|---|---|
| **ITT (N=448)** | **31%** | 38% | -7% | -18.4% |
| **PP (N=427)** | **30%** | 40% | -10% | -25.0% |
| **MAE at 90 Days** | **Impella** | **IABP** | **Difference** | **Relative reduction or increase** |
| **ITT (N=448)** | **37%** | 47% | -10% | -21.3% |
| **PP (N=427)** | **37%** | 49% | -12% | -24.5% |

Table 20b: Composite MACCE at 30 and 90 Days using a contemporary definition for peri-procedural MI (8x ULN) (Intent-to-Treat Population and Per-Protocol Population)

| MACCE at 30 Days | Impella | IABP | Difference | Relative reduction or increase |
|---|---|---|---|---|
| **ITT (N=448)** | **15%** | 19% | -4% | -21.1% |
| **PP (N=427)** | **14%** | 20% | -6% | -30.0% |
| **MACCE at 90 Days** | **Impella** | **IABP** | **Difference** | **Relative reduction or increase** |
| **ITT (N=448)** | **22%** | 30% | -8% | -26.7% |
| **PP (N=427)** | **22%** | 31% | -9% | -29.4% |

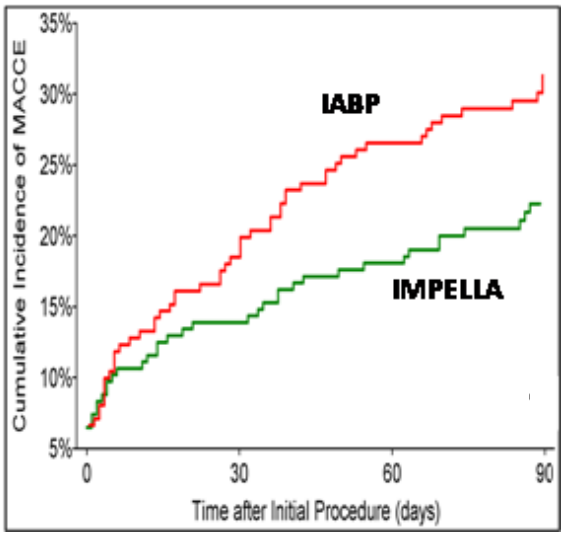
Figure 8a: Additional analysis of the composite MAE and MACCE rates in the Per-Protocol population using a meaningful, contemporary definition for peri-procedural MI (8x ULN).

PP MAE Rates




| MAE | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| PP | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 216 | 174 | 151 | 124 |
| IABP Patients At Risk | 211 | 167 | 129 | 103 |

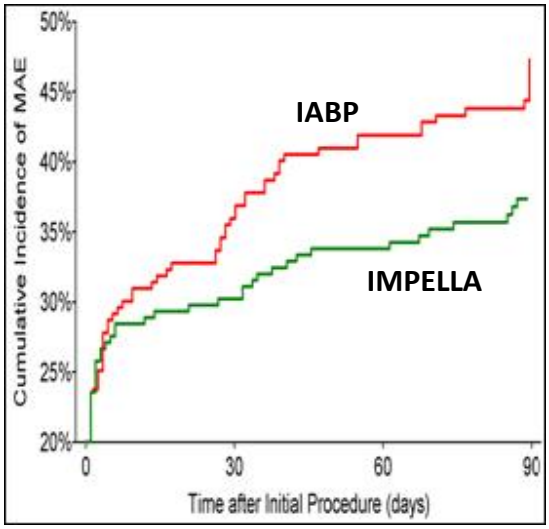
PP MACCE Rates




| MACCE | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| PP | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 216 | 202 | 185 | 153 |
| IABP Patients At Risk | 211 | 197 | 169 | 135 |

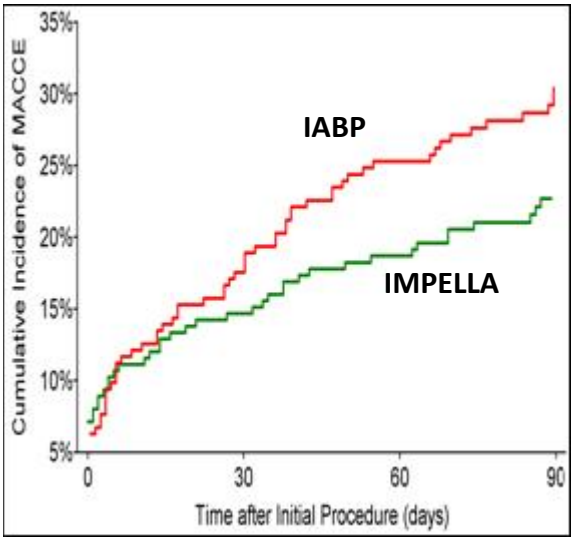
Figure 8b: Additional analysis of the composite MAE and MACCE rates in the Intent-to-Treat population using a meaningful, contemporary definition for peri-procedural MI (8x ULN).

ITT MAE Rates




| MAE | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| ITT | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 225 | 180 | 156 | 129 |
| IABP Patients At Risk | 223 | 178 | 138 | 111 |

ITT MACCE Rates




| MACCE | Time after Initial Procedure (days) | | | |
|---|---|---|---|---|
| ITT | 0 | 30 | 60 | 90 |
| Impella Patients At Risk | 225 | 209 | 191 | 159 |
| IABP Patients At Risk | 223 | 208 | 178 | 143 |

## B. USpella Registry

ABIOMED opened a voluntary registry (USpella) for Impella use in the U.S. for all of its Impella devices, including the Impella 2.5 System. Data is collected at all participating sites retrospectively without pre-selection of patients, and included high risk PCI patients treated with the Impella 2.5 System (albeit from a broader high risk PCI patient population than defined in the PROTECT II Study). The PROTECT II criteria was superimposed on this group of data and yielded an analysis containing 637 patients. These Impella 2.5 System registry data were used as supplemental informative clinical data for FDA review of the Impella 2.5 System PMA P140003, within context of the indications for use.

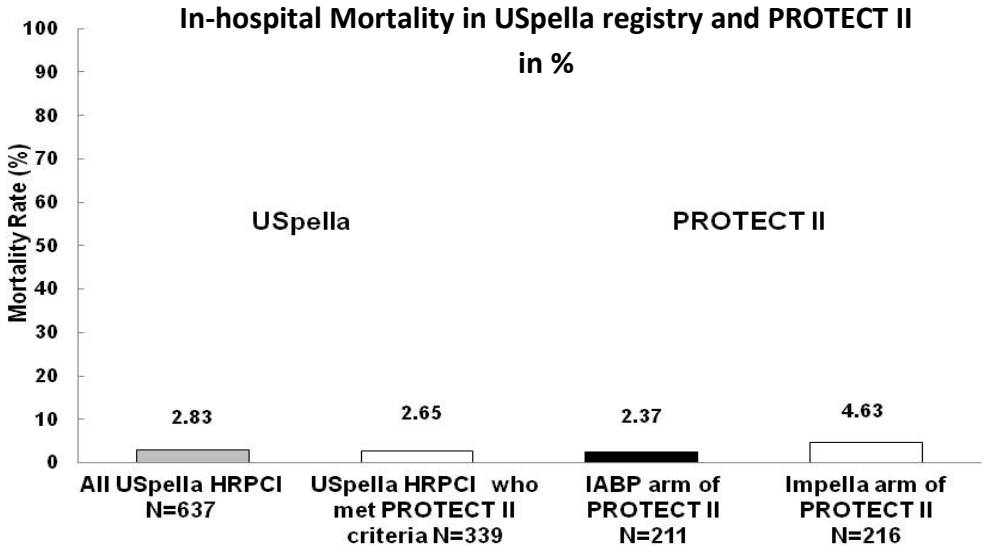
Outcomes and Limitations

Considering the retrospective nature of the registry design, there is a risk for some adverse events to not be documented. This is particularly true for adverse events that were defined based on temporal profile of biomarkers (such as cardiac or renal biomarkers) that require, regular, and periodic monitoring of the blood samples which may not be performed as frequently (if at all) during routine care across institutions.

Other events such as the frequency of hypotensive events may also be not properly documented if accounted for retrospectively based on patient chart review.

However, mortality outcomes are relevant to report and compare to the PROTECT II trial for the following reasons: 1) USpella outcomes to discharge were obtained for 100% of the patients; and 2) death is very likely to be known and reported if the patient expired within the index hospitalization; and 3) USpella data could provide a real word estimate of the potential expected mortality for patients that are deemed to require hemodynamic support with the Impella 2.5 System while undergoing high risk PCI. Mortality outcomes in USpella are depicted in Figure 9. Benchmark with PROTECT II data is also provided.

Figure 9: In hospital mortality for "All USpella HRPCI patients", "All USpella HRPCI patients who met PROTECT II criteria", PROTECT II patients ( IABP and Impella 2.5 System).




Mortality was similar between the USpella subsets and PROTECT II Impella 2.5 System arm and IABP arm. This supports the observation in the PROTECT II trial (448 patient cohort) that there was no increased risk for mortality associated with the use of Impella and large bore access sheath compared to IABP.

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

This PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation. The device has been marketed via 510(k) since 2008 and FDA review of the PMA data supporting the new indication did not raise significant new questions or concerns that needed to be addressed by the Panel.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Safety Conclusions

The results from the pre-clinical laboratory studies performed on the Impella 2.5 demonstrate that the device is suitable for its intended use. The PROTECT II clinical study's secondary safety endpoint demonstrated that it was at least as safe as the IABP control device, which is cleared for use for a similar patient population, for each of ten (10) Serious Adverse Events (SAEs), which were tracked in the study. An assessment of the overall risks related to the Impella 2.5 System were judged to be similar to the IABP.

### B. Effectiveness Conclusions

In the clinical results presented above (PROTECT I, PROTECT II and USpella) Impella 2.5 System appears to show improved hemodynamic support for the patients compared to IABP, as shown by maximal decrease in cardiac power CPO (-0.04±0.24 vs. -0.14±0.27 Watts), which in turn may have allowed more aggressive percutaneous revascularization procedures than would otherwise have been achieved.

Clinical benefit can be implied by the following comparisons:

- An 18.7% relative reduction in the Composite rate of Major Adverse Events at 30 days and 21.6% relative reduction at 90 days as compared to IABP in the Per Protocol Population.
- A 7.9 % absolute reduction in the Composite rate of Major Adverse Events at 30 days as compared to IABP
- An 11.0% absolute reduction in the Composite rate of Major Adverse Events at 90 days as compared to IABP.
- A 29.4% relative reduction in MACCE rates at 90 days as compared to IABP in the Per-Protocol Population when using the more contemporary definition of peri-procedural myocardial infarction (8x ULN).
- A 9.1%.absolute reduction in MACCE at 90 days as compared to IABP in the Per-Protocol Population when using the more contemporary definition of peri-procedural myocardial infarction (8x ULN).

Use of the device in a comparable patient group, as collected retrospectively via ABIOMED's USpella database, showed results similar to those obtained in the PROTECT II clinical trial for overall patient outcomes and hemodynamic support during use.

In conclusion, given the totality of the information available for the Impella 2.5 System, the data suggests that an observed beneficial therapeutic effect at 90 days likely exists in patients undergoing high risk interventions (i.e., patients have few

if any other treatment options due to the severity of the underlying coronary artery disease and co-morbidities).. This beneficial effect is possibly attributable to the ability to perform more aggressive percutaneous revascularization procedures while being supported by the Impella 2.5 System without significantly increasing safety risks, thereby decreasing the late need for symptom driven coronary artery re-intervention.

### C. Benefit-Risk Conclusions

The probable benefits of the device are based on pre-specified and *post hoc* analyses of the data collected in the PROTECT II clinical study. The benefits of the Impella 2.5 System include the potential for improved intra-procedural hemodynamic performance and reduced MAEs (as calculated from a composite of 10 SAEs) at 90 days, as compared to an IABP device.

The probable risks of the Impella 2.5 System were evaluated during the PROTECT II study via the 10 MAEs chosen. The major complications seen during the study were myocardial infarction, hypotension, cardiopulmonary resuscitation (CPR) or ventricular arrhythmia, death and acute renal dysfunction. The rates of these complication rates, are listed in Table 19a and 19b, and were similar for the Impella 2.5 System and the IABP.

In conclusion, given the available information above, the data suggest that, for the Impella 2.5's proposed indication, the probable benefits outweigh the probable risks.

### 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 March 23, 2015.

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:

***New Enrollment Study***: *The study will characterize the post market Impella 2.5 system outcomes at discharge and 90 days relative to a performance goal (PG) which is derived from the PROTECT II study, and will study the outcomes associated with the learning curve. This study will be a prospective, multicenter, single-arm study comprised of 369 participants from 70 US sites supported with the Impella 2.5 system and consented to one year of clinical follow-up. The inclusion and exclusion criteria for the study population will be the same as the PROTECT II population.*

*The primary endpoint for safety and effectiveness will be the 10-component major adverse events (MAE) at 90 days compared to the established PG. The 10 components are: 1) death, 2) stroke/transient ischemic attack (TIA), 3) myocardial infarction (MI), 4) repeat revascularization, 5) cardiac operation or thoracic or abdominal vascular operation or vascular operation for limb ischemia, 6) acute renal dysfunction, 7) cardiopulmonary resuscitation or ventricular arrhythmia requiring cardioversion, 8) increase in aortic insufficiency by more than one grade, 9) severe hypotension (defined as: systolic blood pressure or augmented diastolic pressure [whichever is greater] <90mmHg for ≥5 min requiring inotropic/pressor medications or intravenous fluid), 10) failure to achieve angiographic success defined as residual stenosis <30% after stent implantation. This data will be collected at discharge, 90 days, and one year follow up. The established PG is 53%, which is the upper bound of 95% confidence interval of the 45% point estimated rate.*

*The secondary endpoints include: 1) individual outcomes for each of the 10 MAE components; 2) in-hospital effectiveness and safety endpoints consisting of the effectiveness of hemodynamic support assessed by maximal decrease of cardiac power output from baseline, creatinine clearance change from baseline 24 hours post percutaneous coronary interventions (PCI), device failure assessed as Impella flow <1L/min for more than 5 minutes at the performance level 5 or higher (out of 9), and rate of in-hospital major adverse events; 3) pre-specified subgroup analyses of each of the 10 MAE components, including assessment of the use of adjunctive atherectomy (with versus without), coronary anatomy (unprotected left main/last patent conduit versus 3-vessel disease), morbidity risk (Society of Thoracic Surgery (STS) risk <10 versus ≥10), and learning curve effect.*

*For the composite primary and all secondary individual MI endpoints, the following definitions should be used: 1) peri-procedural MI's (those detected within 72 hours of the procedure) should use a more contemporary definition of peri-procedural MI, i.e. using 8x upper limit of normal (ULN) increase in enzyme release; and 2) all other MI's after 72 hours should use the standard spontaneous MI definition in American Heart Association (AHA) guidelines (i.e. >99% ULN). The total number of MI's at any time interval would be the total of the above two. The individual rates of each MI (early peri-procedural and late spontaneous) is also recommended to be reported.*

*Additional endpoints include 1) procedural safety (composite at 30 days), death, stroke or TIA, need for vascular operation, peri-procedural MI (using >8x ULN), transfusion >2 units or documented hemolysis requiring transfusion >2 units, increase in aortic insufficiency >1 grade, and acute renal dysfunction; 2) procedure effectiveness (composite at 30 days), i.e. alive with none of the procedural hypotension requiring treatment, or failure to achieve angiographic success, or intra-procedural cardiopulmonary respiration or cardioversion; and 3) long-term effectiveness (composite at 90 days and 1 year), i.e. alive with improvement from baseline (pre-procedural) in Canadian Cardiovascular Society angina score from 30 days to measurement time point and none of these (MI using standard spontaneous MI, repeat rehospitalization for unstable angina, or repeat revascularization (PCI or coronary artery bypass).*

## 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