SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Aortic Stent

Device Trade Name: Cheatham Platinum (CP) Stent System
(CPStent – Model 425
Covered CP Stent – Model 427
Mounted CP Stent – Model 426
Covered Mounted CP Stent – Model 428
BiB Stent Placement Catheter – Model 420/420.1)

Device Procode: PNF

Applicant's Name and Address: NuMED, Inc.
2880 Main Street
Hopkinton, NY 12965

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150028

Date of FDA Notice of Approval: March 25, 2016

II. INDICATIONS FOR USE

The CP Stent and Mounted CP Stent are indicated for use in the treatment of native and/or recurrent coarctation of the aorta involving a compliant aortic isthmus or first segment of the descending aorta where there is adequate size and patency of at least one femoral artery and the balloon angioplasty is contraindicated or predicted to be ineffective.

The Covered CP Stent and Covered Mounted CP Stent are indicated for use in the treatment of native and/or recurrent coarctation of the aorta involving the aortic isthmus or first segment of the descending aorta where there is adequate size and patency of at least one femoral artery associated with one or more of the following:

- acute or chronic aortic wall injury
- nearly atretic descending aorta of 3 mm or less in diameter
- a non-compliant stenotic aortic segment found on pre-stent balloon dilation
- a genetic or congenital syndrome associated with aortic wall weakening or ascending aortic aneurysm

III. CONTRAINDICATIONS

1. Patients too small to allow safe delivery of the stent without compromise to the systemic artery used for delivery;
2. Unfavorable aortic anatomy that does not dilate with high pressure balloon angioplasty;
3. Curved vasculature;
4. Occlusion or obstruction of systemic artery precluding delivery of the stent;
5. Clinical or biological signs of infection;
6. Active endocarditis;
7. Known allergy to aspirin, other antiplatelet agents, or heparin;
8. Pregnancy

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CP Stent, Mounted CP Stent, Covered CP Stent, Covered Mounted CP Stent, and BIB Stent Placement Catheter labeling.

V. DEVICE DESCRIPTION

The NuMED Cheatham Platinum (CP) Stent System includes a bare or covered CP Stent and a delivery catheter (BIB). Each stent is balloon expandable and intended for permanent implant. The device is available in the following configurations: The bare stent un-mounted (Cheatham Platinum (CP) Stent), bare stent mounted on delivery catheter (Mounted Cheatham Platinum (CP) Stent), covered stent un-mounted (Covered Cheatham Platinum (CP) Stent, and covered stent mounted on delivery catheter (Covered Mounted Cheatham Platinum (CP) Stent). Each configuration is available in the sizes listed in Table 1.

Table 1. Device Size Matrix

Configuration (number of zigs)	Platinum Wire Diameter (inch)	Diameter (mm)	Labeled Stent Length (mm)					
			16	22	28	34	39	45
8	0.013	12	✓	✓	✓	✓	✓	✓
		14	✓	✓	✓	✓	✓	✓
		15	✓	✓	✓	✓	✓	✓
		16	✓	✓	✓	✓	✓	✓
		18	✓	✓	✓	✓	✓	✓
		20	✓	✓	✓	✓	✓	✓
		22	✓	✓	✓	✓	✓	✓
		24	✓	✓	✓	✓	✓	✓

The CP stent (Figure 1) is composed of a platinum/iridium wire that is arranged in a “zig” pattern, laser welded at each joint and over brazed with 24K gold. Each row of zigs is laser-welded to the next identical row in a repeating manner to accommodate the desired length of the stent. The number of rows determines the unexpanded length of the stent. The CP Stent is balloon expandable and intended for permanent implant.

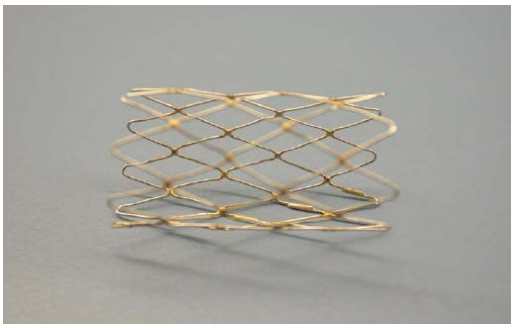

Figure 1. Expanded Bare NuMED CP Stent

The Mounted CP Stent (Figure 2) is the CP Stent mounted on the NuMED BIB balloon expandable catheter.

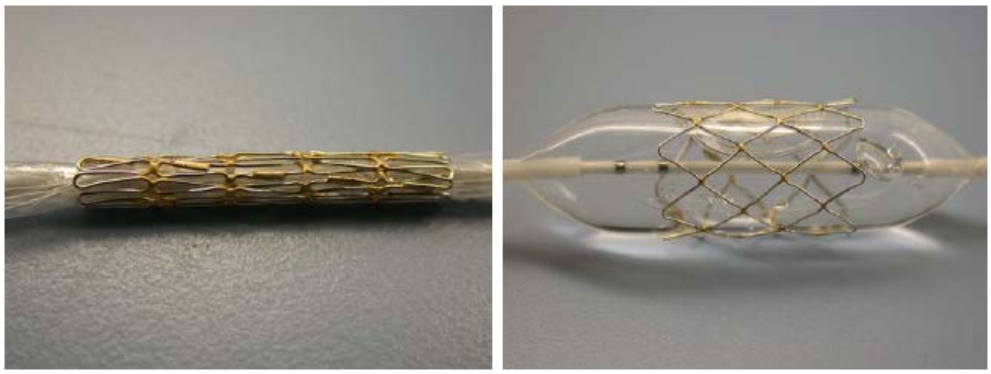

Figure 2. Left: Mounted NuMED CP stent crimped
Right: Mounted NuMED CP stent expanded.

The Covered CP Stent (Figure 3) is comprised of the CP Stent that is covered with an expandable sleeve of ePTFE. The sleeve covers the entire length of the stent. The sleeve is attached to each end of the stent with a cyanoacrylate adhesive on a physically etched section of the sleeve. Upon balloon expansion of the stent, the covering remains intact and expanded with the stent to create a barrier around the stent.

Figure 3. Left: Expanded Covered NuMED CP stents
Right: Hand crimped Covered NuMED CP stents

The Covered Mounted CP Stent (Figure 4) is the Covered CP Stent mounted on the NuMED BIB balloon expandable catheter.

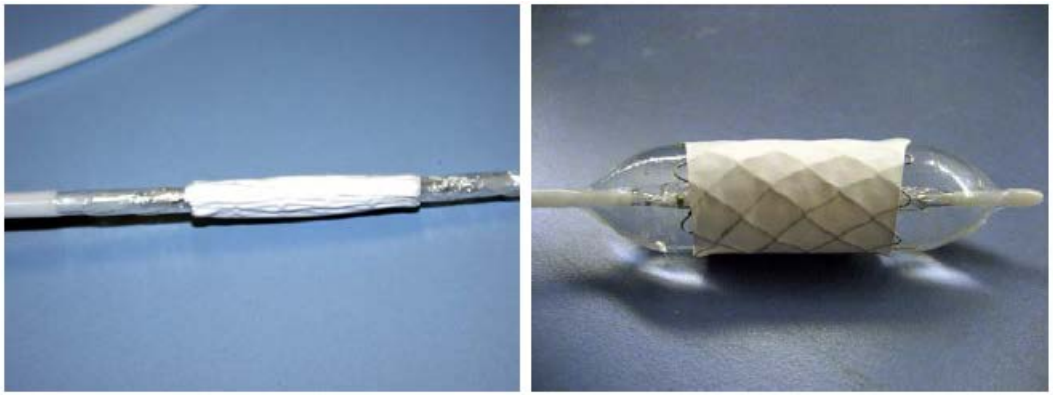

Figure 4. Left: Covered Mounted NuMED CP stent crimped
Right: Covered Mounted NuMED CP stent expanded.

The catheter is triaxial in construction with two lumens being used to inflate the balloons while one lumen is used for tracking over a guidewire. The double balloon catheter allows for incremental inflation for the purpose of dilating a stent. Radiopaque platinum marker bands are located under the balloon shoulders for placement using fluoroscopy. The catheter is composed of PES2, Pebax, Platinum/Iridium, and PES2 with colorants. The delivery catheter is compatible with 0.035" guidewires and 8-11 Fr introducers.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the correction of coarctation of the aorta, including: balloon catheter dilatation and surgical intervention. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CP andCovered CP Stent Systems and BiB Stent Placement Catheter are currently marketed in the following countries:

Table 2. Device Marketing Locations

Product	Countries
CP Stent	Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Columbia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, India, Israel, Jordan, Kenya, Kuwait, Malaysia, Mauritius Island, Mexico, Mongolia, New Zealand, Norway, Pakistan, Peru, Russia, Saudi Arabia, South Africa, Sultanate of Oman, Switzerland, Trinidad & Tobago, Turkey, Uganda, Uruguay, Vietnam.
Covered CP Stent	Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Columbia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, India, Israel, Jordan, Kenya, Kuwait, Malaysia, Mauritius Island, Mexico, Mongolia, New Zealand, Norway, Pakistan, Peru, Russia, Saudi Arabia, South Africa, Sultanate of Oman, Switzerland, Trinidad & Tobago, Turkey, Uganda, Uruguay, Vietnam.
Mounted CP Stent	Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Columbia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, India, Israel, Jordan, Kenya, Kuwait, Malaysia, Mauritius Island, Mongolia, Norway, Pakistan, Peru, Saudi Arabia, South Africa, Sultanate of Oman, Switzerland, Trinidad & Tobago, Turkey, Uganda, Uruguay, Vietnam.
Covered Mounted CP Stent	Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Columbia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, India, Israel, Jordan, Kenya, Kuwait, Malaysia, Mauritius Island, Mongolia, Norway, Pakistan, Peru, Saudi Arabia, South Africa, Sultanate of Oman, Switzerland, Trinidad & Tobago, Turkey, Uganda, Uruguay, Vietnam.

BIB Stent Placement Catheter	Algeria, Argentina, Australia, Bahamas, Brazil, Brunei, Canada, Chile, Columbia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, European Union, Guatemala, Honduras, Hong Kong, India, Israel, Jordan, Kenya, Kuwait, Malaysia, Mauritius Island, Mongolia, New Zealand, Norway, Pakistan, Peru, Russia, Saudi Arabia, South Africa, Sultanate of Oman, Switzerland, Taiwan, Trinidad & Tobago, Turkey, Uganda, Uruguay, Vietnam.

The device has not been withdrawn from marketing for any reason related to its safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Femoral Artery injury, thrombosis or psuedoaneurysm
- Stent Migration
- Stent Stenosis
- Stent Fracture
- Aortic Aneurysm/Pseudoaneurysm
- Aortic Rupture/Tear
- Stent Malposition
- Hematoma
- Sepsis/infection
- Thrombosis/Thromboembolism
- AV fistula formation
- Death
- Transitory arrhythmia
- Endocarditis
- Bleeding
- Cell necrosis at the site of implant
- Cerebrovascular Incident
-

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. *In vitro* Product Testing

Bench testing was performed on the CP Stent and Covered CP Stent as described below. The samples were exposed to 2X Ethylene Oxide sterilization cycle prior to testing. All applicable testing for each stent configuration and the BIB catheter was conducted with accessories representative of clinical use. Testing was conducted according to four corners of the available device unless otherwise noted. A matrix of tests performed and corresponding results are provided in Tables 3 to 5.

Table 3. Summary of *in vitro* Product Testing for CP Stent and Covered CP Stent

Test	Purpose/ Objective	Test/Reference Articles	Results
Material Characterization			
Material Composition	To identify the materials of construction of the stent and delivery system	Test: Two wire bundle samples	All data demonstrated that materials were free from contamination, discoloration and any form of damage that could impact the material. The major elements found were platinum and iridium.
Mechanical Properties	To confirm the ultimate tensile strength (UTS), yield strength (YS) and elongation of the raw material	Test: Raw material wire samples	All data demonstrated that the UTS and wire diameter of the raw material met the acceptance criteria, as confirmed in the Certificate of Conformance from the material manufacturer.

Stent Structural Performance Evaluation			
Corrosion Resistance	To address the corrosion resistance of the stent including pitting, fretting, crevice and galvanic, as appropriate	Test: 6 units of CP 8 Zig 4.5cm	All data demonstrated that the device will not be susceptible to pitting or corrosion.
Stress Analysis (FEA)	To demonstrate the range of stresses at critical locations on the stent during physiological loading	Modeling based on the stent material properties and geometries	All data demonstrated that the Fatigue Analysis and Goodman Diagram predicts the fatigue safety factor to be 1.2 throughout the area of the stent with tensile stress.
Stent Fatigue	To determine the fatigue stresses of the inflated stent design when subjected to fluctuating external pressures	Modeling based on the stent material properties and geometries	All data demonstrated that the Fatigue Analysis and Goodman Diagram predicts the fatigue safety factor to be 1.2 throughout the area of the stent with tensile stress.
Accelerated Durability Testing	To determine the long term durability of the stent	Test: 16 units of CP Stent 8 Zig 4.5cm	All stents survived the durability testing of 400 million cycles in the fatigue testers that applied cyclic pulsatile stresses, simulating the radial strain of

			an artery.
Stent Dimensional And Functional Attributes			
Dimensional Verification	To ensure that all dimensional specifications do not deviate from the design specifications	Test: 10 units of CP Stent 8 Zig in each of the following sizes: 1.6cm, 2.2cm, 2.8cm, 3.4cm, 3.9cm, 4.5cm	All stents met the acceptance criteria and the data showed no deviation from the design specifications.
Percent Stent Area	To determine the contact area of the stent structure, as a percentage of the conceptual solid circumferential area	Test: 1unit of 8 Zig 1.6 cm stent, 1unit of 8 Zig 4.5cm	There is no established criteria for this test, values are calculated and reported. Using ASTM F2081 to define the full cylindrical side surface area for the stents, the percent stent area for CP8Z16 at 12mm is 49% and CP8Z45 at 24mm is 35%.
Stent Foreshortening	To demonstrate the decrease in length of the stent between the catheter loaded condition and deployment to the maximum diameter per the IFU, determining the maximum nominal diameter for which the device is designed	Test: 10 units of the CP Stent mounted on BIB 8 Zig 1.6 cm, 10 units of the CP Stent mounted on BIB 8 Zig 4.5cm, 5 units covered CP 8 Zig 4.5cm	There is no established criteria for this test, values are calculated and reported. The average stent foreshortening of CP8Z16 was 36.4% and of CP8Z45 was 34.9%.
Stent Recoil	To determine the decrease in diameter of the stent, from the maximum balloon expanded condition per IFU	Test: 10 units of CP 8 Zig 1.6 cm stent, 10 units of CP 8 Zig 4.5cm, 5 random lengths of each Covered CP Stent having a diameter of 12, 14, 15, 16, 18, 20, 22, and 24mm	All stents met the acceptance criteria, namely that the stent recoil did not exceed 3.5%.

	to the balloon deflated conditions		
Uniformity of Expanded Diameter	To ensure that the uniformity of the expanded stent is consistent with the labeled expanded diameter	Test: 10 units of CP 8 Zig 4.5cm at 12mm diameter, 10 units of CP 8 Zig 4.5 cm at 24mm diameter: 1.6, 2.2, 2.8, 3.4, 3.9, and 4.5cm Test: 10 units of Covered CP Stent 8 Zig in each of the following sizes diameter: 1.6, 2.2, 2.8, 3.4, 3.9, and 4.5cm	All stents deployed uniformly in each case without significant diameter changes along the length of the stent.
Stent Integrity	To examine deployed stents for damage (cracks/scratches) caused by manufacture, load, and crimp roll down or by deployment/expansion	Test: 10 units of CP Stent mounted on BIB 8 Zig 4.5cm	All data demonstrated that there was no damage to the stents.
Radial Stiffness and Radial Strength	To determine the radial stiffness and the pressure at which irrecoverable deformation occurs	Test: 10 units of CP Stent 8 Zig 2.8cm, 10 units of CP Stent 8 Zig 3.4cm , 1 unit of BIB Catheter 15mm, 1 unit of BIB Catheter 33mm	All samples deformed similarly and without damage.
Radiopacity	To determine the visibility of the stent on real-time and plane film x-ray	Test: 1 unit of CP Stent 8 Zig 3.9cm	All stents were visible on real time and plane film x-ray under x-rays generated 70kV and 57µA.

Table 4. Design Specific Testing for Covered/Covered Mounted CP Stent

Test	Purpose	Test/Reference Articles	Results
ePTFE Permeability/Leakage	To determine the physical properties of the covering material	Test: Raw ePTFE material	The physical properties of ePTFE, including porosity, water

			permeability, and leakage, were defined.
ePTFE Bond Strength	To determine the covering attachment strength	Test: 10 Covered CP stents of various lengths were tested for covering attachment strength	All stent coverings remained attached to the wire framework at bond points.

Table 5. BIB Delivery Catheter Compatibility Testing

Test	Purpose	Test/Reference Articles	Results
Balloon and CP Stent Burst Pressure	To demonstrate the burst strength of the catheter	Test: 20 units of CP Stent 8 Zig 1.6cm with 12 x 2.5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 12 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 14 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 15 x 5 BIB, 20 units CP Stent 8 Zig 4.5cm with16 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 18 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 20 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 22 x 5 BIB, 20 units of CP Stent 8 Zig 1.6cm with 24 x 3 BIB, 20 units of CP Stent 8 Zig 4.5cm with 24 x 5 BIB	All data supported that statistically the balloons will not burst at or below the maximum recommended rated burst pressure.
Balloon Compliance	To demonstrate the stent ID versus inflation pressure characteristics	Test: 20 units of CP Stent 8 Zig 1.6cm with 12 x 2.5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 12 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 14 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 15 x 5 BIB, 20 units CP Stent 8 Zig 4.5cm with16 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 18 x 5 BIB, 20 units of CP Stent 8 Zig 4.5cm with 20 x 5 BIB, 20 units of CP	All data met the acceptance criteria that the inside diameter of the stent shall be +/- 10% of the rated balloon diameter at rated pressure.

		Stent 8 Zig 4.5cm with 22 x 5 BIB, 20 units of CP Stent 8 Zig 1.6cm with 24 x 3 BIB, 20 units of CP Stent 8 Zig 4.5cm with 24 x 5 BIB	
Balloon Fatigue	To determine the repeatability of successful balloon inflations to the RBP	Test: 30 units of CP Stent 8 Zig 1.6cm with 12x2.5 BIB, 30 units of CP Stent 8 Zig 4.5cm with 12x5cm BIB, 30 units of CP Stent 8 Zig 1.6cm with 24x3 BIB, CP Stent 8 Zig 4.5cm with 24x5 BIB	All catheters passed the acceptance criteria, with no failures including loss of pressure or bust at rated burst pressure.
Balloon Inflation/Deflation	To ensure that the catheter inflates and deflated within a specified time	Test: 10 units of CP Stent 8 Zig 1.6cm with 12x2.5BIB, 10 units of CP Stent 8 Zig 4.5 cm with 12x5 BIB, 10 units of CP Stent 8 Zig 1.6cm with 24x3BIB, 10 units of CP Stent 8 Zig 4.5cm with 24x5BIB	All BIBs met the acceptance criteria of a 15second inflation time and 25 second deflation time.
Balloon Deflatability	To ensure that the catheter deflates without interference	Test: 10 units of CP Stent 8 Zig 1.6cm with 12x2.5BIB, 10 units of CP Stent 8 Zig 4.5 cm with 12x5 BIB, 10 units of CP Stent 8 Zig 1.6cm with 24x3BIB, 10 units of CP Stent 8 Zig 4.5cm with 24x5BIB	All BIBs met the acceptance criteria with no interference with balloon deflation.
Catheter Bond Strength	To demonstrate the pull strength of the following: distal hub to extension, extension to “Y” connector, “Y” connector to shaft, proximal balloon bond, tip to balloon	Test: 10 8F, 10 9Fr	All samples exceeded the minimum pull strength of 8.9 Newtons.
Crossing Profile	To measure the crossing profile as the maximum diameter over the length from the proximal end of the mounted stent to	Test: 10 catheters of each balloon diameter were tested with a mounted stent of random length, 3 catheters of each balloon diameter was tested with a covered mounted stent of	All catheters passed through the appropriate Mullins sheath.

	the distal tip of the delivery system	random length	
CP Stent Securement on BIB Delivery Catheter	To ensure that the stent remains intact and is not dislodged while being passed through the tortuous pathway	Test: 10 units of CP Stent 8 Zig 1.6cm with 12x2.5BIB, 10 units of CP Stent 8 Zig 4.5 cm with 12x5 BIB, 10 units of CP Stent 8 Zig 1.6cm with 24x3BIB, 10 units of CP Stent 8 Zig 4.5cm with 24x5BIB	No stents dislodged while passing through passageway.

2. MRI Compatibility

Nonclinical testing and modeling of this device in magnetic fields of 1.5 and 3.0 Tesla showed that the device is MR Conditional. The Bare CP Stent, Bare Mounted CP stent, Covered CP stent, and Mounted Covered CP stent can be scanned safely under the following conditions:

- Static magnetic field of 1.5 T and 3 T
- Maximum spatial gradient magnetic field of 2500 gauss/cm (25 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of scanning (Normal Operating Mode)

3. Biocompatibility

The biological safety assessment of the CP Stent, Mounted CP Stent, Covered CP Stent, Covered Mounted CP Stent and the BIB catheter were conducted in accordance with ISO 10993 standard series "Biological Evaluation of Medical Devices." Each stent in the CP Stent family is classified, per ISO 10993-1, as blood-contacting, permanent (> 30 days) implant devices. Based on the results of the biocompatibility testing performed and leveraged, along with consideration of the extensive clinical use of the stent in the field, the CP Stent family and BIB catheter were determined to be biocompatible. The mounted and un-mounted stents are identical given that the only difference is that the mounted stents are crimped onto the BIB catheter. The Covered CP Stent is considered the worst case in comparison to the bare CP Stent. Thus, the biocompatibility of the Bare CP Stent, Mounted CP Stent, Covered CP Stent, and Covered Mounted CP Stent was assessed with the covered stent. Carcinogenicity testing for the CP Stent family was leveraged from the data contained within the Melody Valve PMA in conjunction with a risk assessment and evaluation of clinical experience. A summary of the testing conducted on the Covered CP Stent and the BIB catheter is provided in Table 6 and 7, respectively.

Table 6. Summary of Biocompatibility Testing for the Covered CP Stent

Test	Objectives	Results
Cytotoxicity (L929)	Assessment of biological reactivity of mammalian cell cultures following incubation with test device extracts	Non-cytotoxic
Sensitization (ISO Guinea Pig Maximization Test)	Determine the potential for the test device extract to elicit contact dermal allergenicity	Non-sensitizing
Irritation (ISO Rabbit Intracutaneous Reactivity)	Assess potential of the device to produce irritation following a single intradermal injection of specific extracts prepared from a test device	Non-irritant
Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluate the adverse effects after a single injection of test device extract	Not systemically toxic
Material-Mediated Pyrogenicity (USP Rabbit Pyrogenicity)	Evaluate the test device extract for leachates that have the potential to induce material-mediated pyrogenicity following a single dose injection	Not pyrogenic
Genotoxicity (AMES)	Evaluate the mutagenic potential of the device test article by measuring its ability to induce DNA reverse mutations in *S. typhimurium* and *E. coli* in the presence and absence of microsomal enzymes	Not-mutagenic
Genotoxicity (Mouse Lymphoma Assay)	Determine the ability of the device test article to induce forward mutations at the thymidine kinase (TK) locus as assayed by colony growth of L5178Y mouse lymphoma cells in the presence of trifluorothymidine (TFT)	Not-mutagenic
Genotoxicity (Mouse Peripheral Micronucleus Study)	Evaluate the potential of the device test article to induce micronuclei formation in immature polychromatic erythrocytes (PCE) present in bone marrow of adult CD-1 mice	Not-mutagenic
Hemocompatibility (Hemolysis)	Determine the percent hemolysis of whole blood following direct contact exposure to the test article	Non-hemolytic
Hemocompatibility (Complement Activation)	*In vitro* evaluation to measure complement activation in normal human serum when serum is exposed to a test article	Not a Sc5b-9 or C3a complement activator
Sub-Chronic Toxicity (ISO Rabbit Subcutaneous Implantation)	Evaluate subchronic systemic toxicity and the local effects of the implant material on living tissue following subcutaneous implantation of the test sample	No toxicity, no irritation
Chronic Toxicity (ISO Rabbit Subcutaneous Implantation)	Evaluate both chronic systemic toxicity and local effects of an implant material on living tissue following subcutaneous implantation of	No toxicity, no irritation

	the test sample	
In Vivo Swine Thrombogenicity	Assess the comparative thromboresistance of the Mounted CP Stent and the Covered Mounted CP Stent by implanting the test articles in the aorta of the swine and comparing thromboresistance with an appropriate control device through gross pathology and a subjective thrombus scoring scale	Non-thrombogenic

A risk assessment of carcinogenic potential of the materials and manufacturing agents of the Covered CP Stent was provided in lieu of carcinogenicity testing. In addition there have been no reported incidences of cancer development associated with the Covered CP Stent that has been marketed for 12 years.

Table 7. Summary of Biocompatibility Testing for the BIB Catheter

Test	Objectives	Results
Cytotoxicity (L929)	Assessment of biological reactivity of mammalian cell cultures following incubation with test device extracts	Non-cytotoxic
Sensitization (ISO Guinea Pig Maximization Test)	Determine the potential for the test device extract to elicit contact dermal allergenicity	Non-sensitizing
Irritation (ISO Rabbit Intracutaneous Reactivity)	Assess potential of the device to produce irritation following a single intradermal injection of specific extracts prepared from a test device	Non-irritant
Systemic Toxicity (ISO Mouse Systemic Injection)	Evaluate the acute adverse effects occurring after a single injection of test device extract	Not systemically toxic
Material-Mediated Pyrogenicity (USP Rabbit Pyrogenicity)	Evaluate the test device extract for leachates that have the potential to induce material-mediated pyrogenicity following a single dose injection	Not pyrogenic
Hemocompatibility (Hemolysis)	Determine the percent hemolysis of whole blood following direct contact exposure to the test article	Non-hemolytic
In Vivo (Canine) Thrombogenicity	Evaluate relative thromboresistance of the materials *in vivo* following an approximate 2 hour implant period	Non-thrombogenic

B. <u>Animal Studies</u>

A non-GLP porcine study was conducted in 2004 to evaluate the safety of the NuMED Cheatham Platinum (CP) Balloon Expandable Stent for use in the treatment of coarctation of the aorta. A summary of this study is provided in Table 8.

Table 8. Summary of Non-GLP Porcine Study

Non-GLP Porcine Study	
Sample Size/Animal Model	Ten 2-3 month old (23-33kg) healthy pigs
Test Articles	11 Bare CP Stents were implanted in ten animals
Technique	Animals were anesthetized. Cardiac catheterization and IVUS imaging was performed to establish appropriate sizing of the CP Stent. Balloons 10% larger than the diameter of the aorta distal to the left subclavian artery were used. Under fluoroscopic guidance a delivery sheath was advanced using a guide wire and the balloon-stent assembly was deployed in the area of interest. Post-deployment imaging was performed and the animals were recovered.
Results	All animals underwent cardiac catheterization and descending aorta angiogram at three months. Stented vessels were dilated if needed using a balloon similar in size to the largest vessel diameter adjacent to the stent. One animal was euthanized at this stage for histopathology of the stented segment At six months cardiac catheterization was again performed for final angiography and IVUS. All animals were terminated at the end of the procedure for necropsy and histopathology of the stented segments. There were no acute complications during implantation. The stent did not inflate symmetrically in one pig, but angiography showed good flow proximal, inside and distal to the stent. At three months all stents were patent; however, two stents were not fully expanded. Both stents were re-expanded. At six months all stents were patent and no significant complications were documented. Histopathology showed all stents to be expanded and vessels to be patent, with significant overexpansion in two of the animals. 90% of the stent struts were endothelialized, with 100% endothelialization in 6 of 11 stents. Approximately 12.7% of all struts and 7/11 stents had at least one strut defined as mal-apposed. Although the overall mean arterial injury score was low, three stents demonstrated deep medial injury or healed medial rupture and 2-3+ inflammation scores at the stent sites. Of these three cases, two had radiographic evidence of significant oversizing. These sites were also associated with significant neointimal thickening. Stent associated inflammation ranged from 0-3+, with 55% of stent sections showing 1-2+ and 45% showing 2-3+. Six of 11 stents had small calcific deposits associated with struts. There was no luminal thrombus deposition noted. Proximal and distal aortic segments were unremarkable. There was an extensive healed medial rupture in one animal which also demonstrated significant stent oversizing.

C. Additional Studies

Sterilization

The CP Stent family is sterilized using Ethylene oxide. The sterilization process has been validated to a sterility assurance level (SAL) of 10^{-6}.

Packaging and Shelf Life

The non-mounted Bare CP Stent and Covered CP Stent are packaged in a small bottle, which is then placed in an inner and outer Tyvek pouch and heat sealed.

The Mounted CP Stent and Covered Mounted CP Stent are packaged in two Tyvek pouches and heat sealed. Over the distal end of the catheter where the stent is mounted, an additional small pouch is placed over the stent to provide extra protection.

The BiB catheter is coiled and placed in two Tyvek pouches and heat sealed.

The shelf life of the CP Stent System has been established at 5 years. Shelf life and package integrity testing was performed on 2x EO sterilized devices that were aged to 5 years using real time aging. Testing demonstrated that the sterility barrier was maintained after 5 years.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of implantation of the Bare CP Stent and Covered CP Stent in the native and/or recurrent coarctation of the aorta in the US under IDE G060057. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies are presented below.

A. Study Design

i. COAST

Patients were treated between February 8, 2008 and November 9, 2010. The database for this PMA reflected data collected through February 1, 2015 and included 112 patients in the safety cohort. Seven patients did not receive a bare metal CP stent, leaving 105 patients in the effectiveness cohort. There were 19 investigational sites.

The study was a prospective, multi-center, single-arm clinical study comparing stent treatment of native or recurrent aortic coarctation to a performance goal (PG) derived from surgical treatment. Surgical PGs are derived from retrospective data collection at selected participating centers and from the literature.

The study used a Data Coordinating Center (DCC) that was responsible for database development, data management, monitoring data quality, monitoring adherence to the protocol by each site, monitoring device accountability, coordinating flow of information to and from the angiographic core laboratory, coordinating activities of the Data and Safety Monitoring Board (DSMB), directing data analysis and complying with FDA regulatory reporting requirements. Core labs were used to independently evaluate angiograms, MR images and angiograms, and fluoroscopic images of the coarctation stent.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the COAST study was limited to patients who met the following inclusion criteria:

Pre-catheterization Inclusion Criteria:

a. Native or recurrent aortic coarctation
b. Weight 35 kg
c. Noninvasive, arm-leg cuff systolic blood pressure* difference or catheter measured systolic coarctation gradient 20 mmHg
*Patients receiving antihypertensive therapy can be included in the study. The type and dose of the medication will be recorded and used for comparisons with follow up evaluations.

Catheterization Inclusion Criteria:

a. Coarctation of the aorta, either native or recurrent that is demonstrated, angiographically to involve the aortic isthmus or first segment of the descending aorta
b. Coarctation of the aorta found to be compliant on pre-stent balloon dilation
c. Patency of at least one femoral artery

Patients were not permitted to enroll in the COAST study if they met any of the following exclusion criteria:

Pre-catheterization Exclusion Criteria:

a. Age > 60 years
b. Connective tissue disorders, including Marfan syndrome and other genetic syndromes such as Turner syndrome and Noonan syndrome
c. Inflammatory aortitis
d. Bloodstream infection, including endocarditis
e. Pregnancy
f. Aortic aneurysm
g. Prior stent placemen
h. Adults lacking capacity to consent
i. Foster children and/or wards of the court

Catheterization Exclusion Criteria

a. Angiography that demonstrates aortic coarctation involving a "curved" region of the aorta, the transverse aortic arch, carotid arterial branches or obstruction extending into or beyond the mid-thoracic descending aorta
b. Complete aortic atresia demonstrated angiographically
c. Anatomic location of coarctation judged by operator to preclude safe placement of a stent
d. Coarctation of the aorta found to be non-compliant on pre-stent balloon dilation

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1 month, 6 months, 12 months, 24 months, and annually to 5 years. Adverse events and complications were recorded at all visits. The preoperative and postoperative assessments are listed in Table 9.

Table 9. Assessment at Follow-up Assessments for COAST

	Pre-Implant Within 3 months prior to implant	In Cath Lab	Pre-D/C	1 month F/U 2 - 6 wks	6 month F/U (4-8 months)	12 month F/U (10-14 months)	24 month F/U (22-26 months)	Annual to 5 years (+/- 3 months)
Screen	X							
Informed Consent	X							
Cardiac Hx/PE	X		X	X	X	X	X	X
Medication History	X			X	X	X	X	X
Paradoxical hypertension		X	X					
Arm-leg systolic BP gradient[1]	X		X	X	X	X	X	X
Echo/Doppler[2]	X		X		X	X		
Fluoroscopy[3]						X	X	X
3D MRI or CT[4]						X	X	**
Adverse Events		X	X	X	X	X	X	X

1.Arm-leg systolic BP gradient at pre-implant must be obtained no more than 4 weeks prior to implantation. For Continued Access patients BPs can be measured as per routine institutional practice with at least one set of 4 quadrant BPs obtained at baseline and at one and two year follow up.
2.Echocardiography is not required for continued access patients.
3.Flouroscopy not required for 3 year follow up.
4.3D MRI scan will be performed to evaluate patient for presence of late aneurysm formation at 1 and 2 years. Additional imaging may be performed on patients with stent fractures, if clinically indicated.

F.2. Data Collection

Data collection for the use of stents will start at time of pre-implant and implant, and will continue at follow-up periods of 1 month, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months after the procedure. Physical exam, Echocardiogram, 3D imaging by MRI or CT scanning or angiography if cardiac catheterization is performed, and adverse events will be collected for

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated:

Primary Safety Endpoint #1: Occurrence of any serious or somewhat serious adverse event attributed to the stent or implantation procedure within 30 days of the catheterization procedure.

The following hypothesis was tested using a one-sample, one-sided test of proportions conducted at the 0.05 level of significance:

$$H_0: p \geq 0.18 \text{ vs. } H_A: p < 0.18$$

Primary Safety Endpoint #2: Occurrence of post-procedure paradoxical hypertension.

The following hypothesis was tested using a two-sided, one-sample test of proportions conducted at the 0.05 level of significance:

$$H_0: p = 0.84 \text{ vs. } H_A: p \neq 0.84$$

With regards to effectiveness, the following criteria were evaluated.

***Primary Effectiveness Endpoint #1*:** Reduction in arm-leg systolic blood pressure gradient from pre-dilation to the 12-month post-dilation follow-up.

Assuming that μ represents the true mean gradient reduction among stent patients, the following hypothesis was tested using a one-sample, one-sided t test conducted at the 0.05 level of significance:

$$H_0: \mu \leq 31 \text{ vs } H_A: \mu > 31$$

***Primary Effectiveness Endpoint #2*:** Length of stay in the hospital, measured in days

The following hypothesis was evaluated using a two-sided, one-sample t test conducted at the 0.05 level of significance:

$$H_0: \mu = 3.5 \text{ vs. HA: } \mu \neq 3.5$$

ii. COAST II

Patients were treated between May 8, 2008 and December 14, 2011. The database for this PMA reflected data collected through February 1, 2015 and included 82 patients. There were 19 investigational sites.

The study was a prospective, multi-center, single-arm clinical study that evaluates the Covered CP Stent for treatment of coarctation of the aorta. For effectiveness, each patient serves as his or her own control. For safety, a performance goal was derived from surgical literature.

The study used a Data Coordinating Center (DCC) that was responsible for database development, data management, monitoring data quality, monitoring adherence to the protocol by each site, monitoring device accountability, coordinating flow of information to and from the angiographic core laboratory, coordinating activities of the Data and Safety Monitoring Board (DSMB), directing data analysis and complying with FDA regulatory reporting requirements. Core labs were used to independently evaluate angiograms, MR images and angiograms, and fluoroscopic images of the coarctation stent.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the COAST II study was limited to patients who met the following inclusion criteria:

Native or recurrent aortic coarctation*associated with one or more of the following:

1. Acute or chronic aortic wall injury**
2. Nearly atretic descending aorta to 3 mm or less in diameter.
3. Genetic Syndromes associated with aortic wall weakening. Individuals with genetic syndromes such as Marfan Syndrome, Turner's Syndrome or familial bicuspid aortic valve and ascending aortic aneurysm.
4. Advanced age. Men and woman aged 60 years or older.

** The significance of aortic obstruction is left to the judgment of the participating investigator. Indications might include mild resting aortic obstruction associated with:*

- *Exercise related upper extremity hypertension;*
- *Severe coarctation with multiple and/or large arterial collaterals;*
- *Single ventricle physiology*
- *Left ventricular dysfunction*
- *Ascending aortic aneurysm*

********Aortic wall injury might include:*

- *Descending aortic aneurysm*
- *Descending aortic pseudo-aneurysm*
- *Contained aortic wall rupture*
- *Non-contained rupture of the aortic wall*

Patients were not permitted to enroll in the COAST II study if they met any of the following exclusion criteria:

a. Patient size too small for safe delivery of the device. The absolute lower limit for inclusion under this protocol is 20 kg. However, serious

femoral artery injury can occur in small patients, particularly those in the 20-30 kg range and this risk must be reviewed in detail with parents or guardians of children in this weight range.

b. Planned deployment diameter less than 10 mm or greater than 22 mm
c. Location requiring covered stent placement across a carotid artery*
d. Adults lacking capacity to consent
e. Pregnancy

**crossing or covering of a subclavian artery is acceptable in certain situations, but only after alternative treatments have been considered.*

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1 month, 6 months, 12 months, 24 months, and annually thereafter to 5 years. Adverse events and complications were recorded at all visits. The preoperative and postoperative assessments are listed in the Table 10.

Table 10. Summary of Follow-up Assessments for COAST II

	Pre-Implant Within 12 wks prior to implant	In Cath Lab	Pre-D/C	1 month F/U (2 - 6 wks)	6 month F/U (4-8 months)	12 month F/U (10-14 months)	24 month F/U (20-28 months)	Annual to 5 years (+/- 4 months)
Screening	X							
Informed Consent	X							
Cardiac Hx/PE	X		X	X	X	X	X	X
Medication History	X			X	X	X	X	X
SIS Assessment	X					X	X	
Arm-leg systolic BP gradient+	X		X	X	X	X	X	X
Fluoroscopy**						X	X	X
3D MRI scan*						X	X	
Adverse Events		X	X	X	X	X	X	X

+ Replicate, four quadrant BPs at baseline, 1 and 2 yrs, with clinical, arm and leg pressure measurements recorded at interim time periods
* If prior stainless steel stent(s) are in place, then CT scanning will be required instead of MRI.
**Fluoroscopy not necessary for the 3 year follow up visit, but is added at 4 and 5 years.

3. Clinical Endpoints

With regards to safety, the following criteria were evaluated.

***Primary Safety Endpoint*:** Occurrence of any serious or somewhat serious adverse event attributed to the stent or implantation procedure within 30 days of the catheterization procedure.

The following hypothesis was tested using a one-sample, one-sided test of proportions conducted at the 0.05 level of significance:

$$H_0: p \geq 0.18 \text{ vs. } H_A: p < 0.18$$

***Secondary Safety Endpoint*:** Proportion of patients experiencing any of the following adverse events related to the device or implant procedure post 1 year

- Underlying cardiac or non-cardiac disease, aortic wall injury, new aortic aneurysm formation within region of device, stent misplacement, malposition, stent fracture, aortic wall aneurysms, or restenosis requiring reintervention.

With regards to effectiveness, the following criteria were evaluated.

***Primary Effectiveness Endpoint #1*:** Improvement of aortic wall injury and/or aortic arch obstruction by a median increase of at least one grade from pre-implantation baseline to 12-month follow-up using the Severity of Illness Scale (based on upper extremity (UE) systolic BP, UE to lower extremity (LE) systolic BP, and aortic wall injury).

The following hypothesis was tested using a one-sided Wilcoxon signed-rank test conducted at the 0.025 level of significance:

H_0: median change in grade ≤ 0 vs. H_A: median change in grade > 0

Primary Effectiveness Endpoint #2: Aortic wall injury and aortic arch obstruction at Grade 4 or above at the 12-month follow-up, based on the Severity of Illness Scale, with no clinical worsening.

The following hypothesis was tested using a one-sample, one-sided test of proportions conducted at the 0.05 level of significance:

$$H_0: p \leq 0.70 \text{ vs. } H_A: p > 0.70$$

Secondary Effectiveness Endpoints:

- Reduction of arm-leg systolic blood pressure gradients to less than 20mmHg and less than 15 mmHg.
- Reduction of upper extremity blood pressure at 1 year compared to baseline
- Repair of wall defect with <10% residual endoleak on MRI or CT in patients with aortic wall injury
- Hospital length of stay compared to length of stay for surgical repair of aortic coarctation.

B. Accountability of PMA Cohort

COAST

Of the 167 enrolled patients, 102 met the study eligibility criteria and were treated with the CP Stent. 112 patients were evaluated for safety, of which 5 patients crossed-over to the Covered CP Stent therapy. Approximately 107 stents were implanted in 105 patients and these patients were included in the evaluation of effectiveness.

At the time of database lock, of 112 safety cohort patients and 105 effectiveness cohort patients, 87 patients were available for analysis at the completion of the study, the 24 month post-operative visit. Study accountability is detailed in Table 11.

Table 11. COAST Accountability

	Possible N (100%)	1 Month Visit n (%)	12 Month Visit n (%)	24 Month Visit n (%)	3 years n (%)	4 years n (%)	5 years n(%)
Safety Cohort	112	102 (91%)	94 (84%)	90 (80%)	80 (71%)	76 (68%)	73 (65%)
Effectiveness Cohort	105*	100 (95%)	92 (88%)	87 (83%)	77 (73%)	69 (66%)	56 (53%)

*112 patients underwent catheterization and pre-stenting balloon angioplasty, five then received Covered CP Stents and were entered into the COAST II trial where they have been followed since. Two patients did not receive study stents and are followed for safety outcomes only.

COAST II

At the time of database lock, of 82 patients enrolled in the PMA study, are available for analysis at the completion of the study endpoints (i.e. the 24 month post-implant visit). Study accountability is detailed in Table 12.

Table 12. COAST II Accountability

COAST II Patients	Possible N (100%)	1 Month Visit n (%)	12 Month Visit n (%)	24 Month Visit n (%)	3 years n (%)	4 years n (%)	5 years n (%)
Safety Cohort	82	82 (100%)	69 (84%)	67 (81.7%)	55 (67.1%)	38 (46.3%)	22 (26.8%)
Effectiveness Cohort	82	82 (100%)	68 (83%)	66 (80.5%)	54 (65.8%)	37 (45.1%)	21 (25.6%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a coarctation of the aorta study performed in the US. The COAST and COAST II demographics are shown in Table 13.

Table 13. COAST and COAST II Patient Characteristics

COAST

Assessment	Number (Percent) or Median (Range)	
	Safety Cohort (n=112)	Efficacy Cohort (n=105)
Gender		
Male	77 (69%)	73 (70%)
Female	35 (31%)	32 (30%)
Age, years	16 (8 to 52)	16 (8 to 52)
NYHA Classification		
I	88 (79%)	82 (78%)
II	22 (20%)	21 (20%)
III	1 (1%)	1 (1%)
IV	1 (1%)	1 (1%)
Primary Indication		
Native Coarctation	65 (58%)	60 (57%)
Recurrent Coarctation	47 (42%)	45 (43%)

COAST II

Assessment	Number (Percent) or Median (Range)		
	Prospective (n=29)	Legacy (n=53)	Total (n=82)
Gender			
Male	21 (72%)	31 (58%)	52 (63%)
Female	8 (28%)	22 (42%)	30 (37%)
Age, years	20 (6 to 67)	17 (6 to 66)	18 (6 to 67)
Primary Indication			
Repair of aortic wall injury	15 (52%)	34 (64%)	49 (60%)
Prevention of aortic wall injury[1]	14 (48%)	19 (36%)	33 (40%)

[1] Includes 1 patient classified as not having pre-existing aortic wall injury, who was noted to have a small, localized intimal tear with a diameter of < ¼ the aortic diameter (study number 013-501).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the implanted cohort of 112 COAST and 82 COAST II patients completing their implant procedures. The primary safety outcomes are presented in Table 14.

Table 14. Summary of COAST and COAST II Outcomes and Pre-Specified Safety Endpoints

	Safety Endpoint	**Event Rate**	**P Value (CI)**
COAST ***Primary***	Serious or Somewhat Serious Adverse event attributed to the Stent or Implantation procedure within 30 days of the procedure	8.9%	0.006 (4.9%, 14.7%)*
	Post-procedure paradoxical hypertension	7.5%	<0.001 (3.3%, 14.2%)[+]
COAST II ***Primary***	Serious or Somewhat Serious Adverse Events Attributed to the Stent, Implantation or Catheterization within 30 days of the procedure (includes data from COAST combined with COAST II)	8.2%	<0.001 (5.2%, 12.3%)*
Secondary	Proportion of patients experiencing any AEs related to the device or implant procedure post 1 year (among 74 patients followed for at least 1 year)	6.8%	N/A (2.2%, 15.1%)[+#]

*90% Confidence interval
[+] 95% Confidence Interval
[#] confidence interval provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The COAST and COAST II primary safety endpoints were met with the occurrence of any serious or somewhat serious adverse event within 30 days post procedure being less than the predefined 18%. Post procedural paradoxical hypertension was observed in 7.5% of patients in the COAST Trial. The COAST primary safety endpoint for the incidence of paradoxical hypertension (< 84%) was met.

Adverse effects that occurred in the PMA clinical study:

The overall incidence and types of adverse events were within expected ranges. Aortic wall injuries were rare and treated appropriately without the need for emergency surgery. The results are durable out to 60 months for each study and re-coarctation was treated by transcatheter means when it occurred. There were no late complications related to device fracture noted, though incidence of stent fracture increased with time for COAST patients. Table 15 provides a summary of the adverse events reported under COAST and COAST II.

Table 15. Summary of Adverse Events (AEs) for COAST

	Stent Related Events[1] (Rates)	**Stent, Implantation, or Catheterization Related Events[2] (Rates)**	**All Events (Rates)**
Patients with adverse events at 30 days	1 (0.9%)	37 (33.0%)	50 (44.6%)
Serious or somewhat serious events at 30 days	1 (0.9%)	10 (8.9%)	11 (9.8%)
Serious or somewhat serious events at 30 days, excluding stent fracture	1 (0.9%)	10 (8.9%)	11 (9.8%)
Serious event at 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with adverse events at 12 Months	4 (3.6%)	40 (35.7%)	69 (61.6%)
Serious or somewhat serious events at 12 months	4 (3.6%)	13 (11.6%)	16 (14.3%)
Serious or somewhat serious events at 12 months, excluding stent fracture	2 (1.8%)	11 (9.8%)	14 (12.5%)
Serious event at 12 months	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients with adverse event at 24 Months	13 (11.6%)	47 (42.0%)	73 (65.2%)

[1]Includes events that are due to or possible due to stent, and stent fractures.
[2]Includes events that are due to or possible due to stent, implantation, or catheterization, and stent fractures

Table 16. Summary of Adverse Events (AEs) for COAST II

	Stent Related Events[1] (Rates)	**Stent, Implantation, or Catheterization Related Events[2] (Rates)**	**All Events (Rates)**
Patients with adverse events at 30 days	2 (2.4%)	27 (32.9%)	42 (51.2%)
Serious or somewhat serious events at 30 days	1 (1.2%)	6 (7.3%)	7 (8.5%)
Serious or somewhat serious events at 30 days, excluding stent fracture	1 (1.2%)	6 (7.3%)	7 (8.5%)
Serious event at 30 days	0 (0.0%)	1 (1.2%)	1 (1.2%)
Patients with adverse events at 12 Months	4 (4.9%)	30 (36.6%)	58 (70.7%)
Serious or somewhat serious events at 12 months	3 (3.7%)	7 (8.5%)	14 (17.1%)
Serious or somewhat serious events at 12 months, excluding stent fracture	3 (3.7%)	7 (8.5%)	14 (17.1%)
Serious event at 12 months	1 (1.2%)	1 (1.2%)	4 (4.9%)
Patients with adverse event at 24 Months	5 (6.1%)	31 (37.8%)	60 (73.2%)

[1]Includes events that are due to or possible due to stent, and stent fractures.
[2]Includes events that are due to or possible due to stent, implantation, or catheterization, and stent fractures

Tables 17 through 19 document the stent related, implantation related and catheterization procedure related adverse events in the COAST and COAST II trials.

Table 17. Stent Related Adverse Events for COAST and COAST II

	Event	**n (Event Rate)**
COAST (n=112)	Aortic Aneurysm	1 (0.9 %)
	Increased cardiac output, tachycardia/light-headedness	1 (0.9 %)
COAST II (n =82)	Aortic Aneurysm	2 (2.4 %)
	Asymmetric Stent Shortening	1 (1.2 %)
	Left arm numbness and weakness	1 (1.2 %)

Table 18. Implantation Related Adverse Events for COAST and COAST II

	Event	n (Event Rate)
COAST (n=112)	Aortic Aneurysm	2 (1.8 %)
	Back Pain	1 (0.9 %)
	Chest Pain	5 (4.5 %)
	Confined Vascular Tear	3 (2.7 %)
	Groin Pain	4 (3.6 %)
	Intimal tear with vessel irregularity	1 (0.9 %)
	Jailed left subclavian	1 (0.9 %)
	Local hematoma groin	1 (0.9 %)
	Pain	1 (0.9 %)
	Right leg pain	1 (0.9 %)
	Stent malposition	1 (0.9 %)
COAST II (n =82)	Aneurysmal formation	1 (1.2 %)
	Chest pain	4 (4.9 %)
	Chest and back pain	1 (1.2 %)
	Easy bruising on aspirin	1 (1.2 %)
	Increased bruising	1 (1.2 %)
	Right groin pain	1 (1.2 %)
	Stent malposition	2 (2.4 %)
	Wound bleeding	1 (1.2 %)

Table 19. Catheterization Related Adverse Events for COAST and COAST II

	Event	n (Event Rate)
COAST (n=112)	AV fistula	1 (0.9 %)
	Bleeding	1 (0.9 %)
	Corneal abrasion	1 (0.9 %)
	Decreased pulse	1 (0.9 %)
	Fever	1 (0.9 %)
	Groin pain	1 (0.9 %)
	Local hematoma groin	4 (3.6 %)
	Right inguinal hematoma	1 (0.9 %)
COAST II (n =82)	Aneurysm	1 (1.2 %)
	Atrial arrhythmia	1 (1.2 %)
	Brachial plexus injury	1 (1.2 %)
	Contact skin rash	1 (1.2 %)
	Corneal abrasion	1 (1.2 %)
	Discomfort right eye	1 (1.2 %)
	Dissection of iliac artery	1 (1.2 %)
	Ecchymosis/groin tenderness	1 (1.2 %)
	Femoral artery occlusion	1 (1.2 %)
	Local hematoma groin	2 (2.4 %)
	Localized groin bruising	1 (1.2 %)
	Minimal bleeding/cough	1 (1.2 %)
	Neck swelling	1 (1.2 %)
	Pulsatile bleeding	1 (1.2 %)
	Right iliac dissection/pulse loss	1 (1.2 %)
	Superficial infection of groin	1 (1.2 %)
	Wide complex non-sustained tachycardia	1 (1.2 %)

There were five patients that crossed over from COAST to COAST II. One patient crossed over due to a small aneurysm after dilation, two patients due to a near atretic aorta, one patient due to localized intimal tear after dilation and one patient due to an acute, rapidly expanding aneurysm after dilation. In the COAST trial, one patient experienced stent malposition, representing 0.9% of patients, and this event was resolved in the catheterization lab with no permanent damage. In the COAST II trial, two patients experienced two events, representing 2.4% of patients, and both events were resolved using a second Covered CP stent to fully occlude the aneurysm developed with no permanent damage.

In the COAST trial, five patients experienced aortic wall injury, four that occurred prior to hospital discharge and one that occurred by 24-month follow-up. These five events are detailed in Table 20, below.

Table 20. COAST Aortic Wall Injuries by 24 Month Follow-up

Patient	Bare Metal CP Stent Implanted	Type of Injury	Outcome of Event
1	No	Small aneurysm after dilation	Cross-over to Covered CP Stent
2	Yes	Therapeutic and localized tear	Resolved after implantation of Bare Metal CP Stent; tear no longer visible and not noted on further imaging
3	Yes	Contained rupture	Possible minimal aneurysm with no progression during admission; not noted on further imaging
4	Yes	Aneurysm	Implantation of Covered CP Stent
5	No	Acute, rapidly expanding aneurysm after dilation	Cross-over to Covered CP Stent

In the COAST II trial, three patients experienced aortic wall injuries by the 24-month follow-up. These injuries are detailed in Table 21, below.

Table 21. COAST II Aortic Wall Injuries by 24 Month Follow-up

Patient	**Injury Detected**	**Intervention**
1	Neo-intimal proliferation	Therapy for new aortic wall injury – implantation of Covered CP Stent
2	Small aneurysm at 12 m visit	Therapy for new aortic wall injury – implantation of Covered CP Stent

3	Small aneurysm at 12 m visit	New Covered CP Stent implanted to occlude aneurysm

In COAST, four patients with events underwent catheter reinterventions, representing 3.7% of patients with an event. No surgical interventions were performed. Table 22 provides a summary of these four interventions.

Table 22. COAST Coarctation-Related Reintervention by 24 Months

Approximate Time to Intervention Post-procedure (Months)	Indication for Reintervention	Procedure Performed
11	Planned reintervention to fully expand stent	Redilation of stent, implantation of non-study stent
20	Planned re-expansion of stent	Redilation of stent
14	Aneurysm detected at 12m visit	Therapy for new aortic wall injury - implantation of Covered CP Stent
14	Planned re-expansion of stent, signs of restenosis at coarctation site	Redilation of stent

In COAST II, six patients experienced coarctation-related events, representing 7.3% of patients with events. These patients underwent catheter reinterventions. No surgical interventions were completed. Table 23 provides a summary of these interventions.

Table 23. COAST II Coarctation-Related Reintervention by 24 months

Approximate Time to Intervention Post-procedure (Months)	Indication for Reintervention	Procedure Performed
7	Persistent hypertension and gradient across aortic arch	Radiation of stent
7	Planned re-expansion of stent	Radiation of stent
9	Planned re-expansion of stent	Radiation of stent
25	Increased gradient with somatic growth; neo-intimal proliferation detected in cath lab	Therapy for new aortic wall injury - implantation of Covered CP Stent
14	Aneurysm detected by MRI at 12 m visit[1]	Therapy for new aortic wall injury - implantation of Covered CP Stent
13	Aneurysm detected by MRI at 12 m visit1	Therapy for new aortic wall injury - implantation of Covered CP Stent

[1.] Presence of aneurysm in this patient was not confirmed by core laboratory review of the MRI

In COAST, two patients experienced non-coarctation related reinterventions that were documented by the 24-month follow-up. These patients underwent surgical interventions. The time to intervention for one patient was 20 months, at which time the patient had an aortic valve replacement to address progressive and severe left ventricular enlargement and progression of exercise intolerance. The time to intervention for the second patient was approximately two months, when the patient received a mitral valve replacement to address mitral regurgitation. In COAST II, two patients experienced non-coarctation

related reinterventions that were documented by the 24 month follow-up, representing 2.4% of the patients with events. These patients underwent catheter reinterventions. The time to intervention for one patient was four months, when the patient received a coronary angiogram and graft angiogram to address symptoms of angina. The time to intervention for the second patient was 26 months when the Melody valve was implanted to address a high right ventricle to pulmonary artery conduit gradient.

Stent fracture was increasingly common during follow-up ranging from 12% at 24 months to 36% at 60 months in patients treated with bare metal stents (COAST trial). However, no loss of structural integrity and no complications resulting in patient injury were observed. The incidence of stent fracture for covered CP stents (COAST II) was much lower and was not observed to substantially increase over time. Also, relief from blood pressure gradient was maintained through 60 month follow-up and re-intervention was rare. When needed, this was accomplished using transcatheter interventions.

Table 24 shows the stent fracture events in the COAST pivotal cohort.

Table 24: COAST Pivotal Cohort –Stent Fracture

	Completed 12 Month Fluoroscopy (n=91)[1]	Completed 24 Month Fluoroscopy (n=87)[3]
Percentage of Eligible Subjects Undergoing Fluoroscopy	91/104[2] (88%)	87/103[4] (84%)
Stent Fracture	2 (2.2%)	11 (12.6%)
No loss of structural integrity	2	11
Loss of structural integrity	0	0

[1] Among 104 eligible subjects, excludes: 1 patient lost to follow-up at 1 month, 2 patients lost to follow-up at 6 months, and 3 patients lost to follow-up at 12 months. An additional 7 patients did not undergo fluoroscopy at 12 months.

[2] Cross-over patients treated with Covered CP Stent (5) were followed only through implantation of Bare Metal CP Stent; intent to treat patients (2) were followed only through hospital discharge. One patient withdrew consent prior to the 12 month visit.

[3] Among 103 eligible subjects, excludes: 6 patients previously lost to follow-up, and 5 patients lost to follow-up at 24 months. An additional 5 patients did not undergo fluoroscopy at 24 months.

[4] In addition to cross-over patients treated with Covered CP Stent, intent to treat patients, and 1 patient who withdrew consent prior to the 12 month follow-up, 1 patient was noted to have an aneurysm at the 12 month visit and was treated using a Covered CP Stent; this patient is no longer followed for COAST and is currently enrolled in COAST II.

A summary of the number of stents implanted in COAST and COAST II enrolled patients who underwent cardiac catheterization for the purpose of Coarctation of the Aorta is provided in Tables 25 and 26.

Table 25: COAST Pivotal Cohort – Procedural Data

	Number (Percent)
	Treated with Bare Metal CP Stent, or Meeting Study Eligibility Criteria but Not Treated with Bare Metal CP Stent (n=107)[1]
Bare Metal CP Stent Implanted	105 (98%)
Second Bare Metal CP Stent Implanted (n=105)	2 (2%)

[1] Includes: Patients treated with Bare Metal CP Stent meeting study eligibility criteria (102), patients treated with Bare Metal CP Stent not meeting study eligibility criteria (3), patients meeting study eligibility but not treated with Bare Metal CP Stent (2).

Table 26: COAST II Pivotal Cohort – Procedural Data

	Number (Percent)
	Total (n=82)
Covered CP Stent Implanted	82 (100%)
Second Covered CP Stent Implanted	9 (11%)
Third Covered CP Stent Implanted	2 (2%)
Patient Free of Explant 24 hours after Procedure	82 (100%)

2. Effectiveness Results

The analysis of effectiveness was based on the 105 COAST patients receiving bare metal CP stents and 82 patients receiving Covered CP Stents in the COAST II study. The key effectiveness outcomes are presented in Tables 27 through 29.

Although the COAST primary effectiveness endpoint for blood pressure gradient reduction was not met, the observed blood pressure gradients were clinically meaningful. Failure to meet the endpoint was a function of the endpoint chosen rather than a failure to achieve reduction of the underlying gradient. From a clinical perspective, relief of systolic blood pressure gradient was complete and sustained.

Table 27. Summary of Late Outcomes and Major Pre-Specified Primary Effectiveness Endpoints

COAST	**Effectiveness Endpoint**	**Event Rate**	**P Value (CI)**
Primary	Mean Reduction in Systolic Blood Pressure Difference, Pre-Dilation to the 12 Month Post-Dilation Follow-Up	30 ±22mmHg	0.64 (26mmHg, 34mmHg)*
	Length of Stay in Hospital	1.1±0.3 days	<0.001 (1.0 days, 1.1 days)[+]
COAST II ***Primary***	Severity of Illness Scale Grade 4 or 5 with No Clinical Worsening at 12 Month Follow-up	80%	0.048 (70.1%, 87%)*
COAST II ***Secondary***	Proportion of patients with arm-leg systolic blood pressure differences less than 20mmHg and less than 15 mmHg at 12 month follow-up, compared to baseline	87% (up from 46% at baseline) 79% (up from 38% at baseline)	p<0.001 (76%, 94%)[+] p<0.001 (68%, 88%)[+]
	Reduction of upper extremity blood pressure at 1 year compared to baseline	12 ±20mmHg	N/A (7mmHg, 17mmHg)[+#]
	Complete repair of aortic wall defect with first Covered CP Stent (no residual endoleak during the catheterization procedure	47 of 49 (96%) of patients treated for an aortic wall injury	N/A
	Proportion of patients with effective treatment of AWI with no residual aneurysm seen on MRI scanning	37 of 39 (95%) patients treated for an aortic wall injury 1/39 (2.5%) with a small aneurysm and one patient's MRI could not be evaluated by core lab	N/A
	Hospital length of stay compared to length of stay for surgical repair of aortic coarctation	1.2 ± 0.9 days	<0.001 (1.0 days, 1.4 days)[+]

*90% Confidence interval

[+] 95% Confidence Interval

[#] Confidence interval provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Table 28. COAST Pivotal Cohort – Systolic Blood Pressure

	Number (Percent) or Median (Range) And Mean ± Standard Deviation		
	Completed 1 Month Follow-up (n=100)[1]	Completed 12 Month Follow-up (n=92)[2]	Completed 24 Month Follow-up (n=87)[3]
Upper Extremity Systolic Blood Pressure (mmHg) Median (range) Mean ± standard deviation	118 (83 to 148) 120 ± 12	122 (82 to 148) 123 ± 12	121 (87 to 175) 122 ± 14
Lower Extremity Systolic Blood Pressure (mmHg) Median (range) Mean ± standard deviation	119 (91 to 163) 122 ± 15	122 (89 to 180) 123 ± 15	123 (84 to 172) 125 ± 16
Systolic Blood Pressure Difference (mmHg) Median (range) Mean ± standard deviation	-1 (-45 to 32) -2 ± 13	-1 (-37 to 40) -1 ± 15	-4 (-46 to 43) -3 ± 15
Reduction in Systolic Blood Pressure Difference Pre-Dilation (n=99[4], 91[5])	31 ± 18	30 ± 22[6]	33 ± 20

[1] Among 104 eligible subjects, excludes: 1 patient lost to follow-up at 1 month. An additional 3 patients missed the 1 month visit.

[2] Among 104 eligible subjects, excludes: 1 patient previously lost to follow-up, 2 patients lost to follow-up at 6 months, and 3 patients lost to follow-up at 12 months. An additional 6 patients missed the 12 month visit.

[3] Among 101 eligible subjects, excludes: 6 patients previously lost to follow-up, and 5 patients lost to follow-up at 24 months. An additional 3 patients missed the 24 month visit.

[4] One patient does not have 1 month systolic blood pressure difference due to missing lower extremity pressure.

[5] One patient does not have 12 month systolic blood pressure difference due to missing lower extremity pressure.

[6] Primary effectiveness outcome.

Table 29. COAST II Pivotal Cohort – Systolic Blood Pressure

	Number (Percent) or Median (Range) And Mean ± Standard Deviation	
	Completed 12 Month Follow-up (n=68)[1]	Completed 24 Month Follow-up (n=66)[2]
Upper Extremity Systolic Blood Pressure (mmHg)		
Median (range)	123 (98 to 166)	126 (96 to 158)
Mean ± standard deviation	125 ± 14	126 ± 13
Lower Extremity Systolic Blood Pressure (mmHg)		
Median (range)	121 (90 to 199)	124 (86 to 156)
Mean ± standard deviation	124 ± 21	125 ± 16
Systolic Blood Pressure Difference (mmHg)		
Median (range)	2 (-48 to 38)	0 (-35 to 62)
Mean ± standard deviation	1 ± 16	1 ± 17
Systolic Blood Pressure Difference		
< 10 mmHg	46 (68%)	52 (79%)
< 15 mmHg	54 (79%)	56 (85%)
< 20 mmHg	59 (87%)	60 (91%)

[1] Among 81 eligible subjects, excludes: 3 patients lost to follow-up at 6 and 4 patients lost to follow-up at 12 months. An additional 6 patients missed the 12 month visit.

[2] Among 80 eligible subjects, excludes: 7 patients previously lost to follow-up, and 2 patients lost to follow-up at 24 months. An additional 5 patients missed the 24 month visit.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: age, gender, and condition. While the early adverse event rate was higher in females, likely due to peripheral artery size differences, the residual gradient not different by gender. These subgroup analyses did not reveal significant differences in treatment outcomes.

In the COAST trial, no subgroup analysis was performed by age. Under COAST II, in a comparison of outcome by age, there was no significant difference in the proportions of patients with a serious or somewhat serious adverse event attributed to the stent or procedure for patients younger or older than 16 years old. A subgroup analysis for gender was completed for COAST and COAST II. The outcome defined as the proportion of patients with a serious or somewhat serious adverse event attributed to the stent or procedure, exhibited a worse trend for females than males, although not statistically different. The remaining outcomes in each study did not present significant differences between genders. A comparison of outcome by

primary indication was performed for the COAST safety cohort. There was no significant difference in outcomes of the safety cohort with native coarctation or recurrent coarctation. There was also no difference in the outcomes of the safety cohort with repair of the aortic wall injury or prevention of aortic wall injury. Also, using the COAST II data, a comparison of outcomes by coarctation minimum diameter was performed and did not demonstrate any difference between the effectiveness cohort with a minimum diameter of ≤ 3.0mm and ≥ 3.1mm.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 2 investigators of which none were full-time or part-time employees of the sponsor and 2 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: 2
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The supplemental clinical data to the PMA application came from the Continued Access studies for COAST and COAST II conducted in the United States. The objective was to collect additional safety and effectiveness data on the CP Stent Family in subjects with aortic coarctation.

A. Study Design

COAST CAP

The COAST Continued Access Protocol was a prospective, multi-center, single-arm clinical study allowing continued access to the CP Stent during regulatory review of the pre-market application for the CP Stent. Up to 19 investigational sites with prior CP Stent experience in the COAST Study were allowed to participate.

The endpoints of the COAST CAP registry were similar to those in the COAST Study but there were no pre-specified statistical hypotheses. The primary safety endpoints were the occurrence of device or implant related serious adverse events and the occurrence of post-procedure paradoxical hypertension. The primary effectiveness endpoints were reduction in arm-leg systolic blood pressure gradient and length of stay in the hospital. All patients were scheduled to return for follow-up examinations at 1 month, 6 months, 12 months, 24 months, and annually to 5 years.

COAST II CAP

The COAST II Continued Access Protocol was a prospective, multi-center, single-arm clinical study allowing continued access to the Covered CP Stent during regulatory review of the pre-market application for the Covered CP Stent. Up to 19 investigational sites with prior Covered CP Stent experience in the COAST II Study were allowed to participate.

The endpoints of the COAST II CAP registry were similar to those in the COAST II Study but there were no pre-specified statistical hypotheses. The primary safety endpoint was the occurrence of device- or procedure- related serious adverse events. The primary effectiveness endpoint was improvement of aortic wall injury and/or aortic arch obstruction. All patients were scheduled to return for follow-up examinations at 1 month, 6 months, 12 months, 24 months, and annually to 5 years.

B. **Accountability of Non-Pivotal Trials**

COAST CAP

Sixteen patients underwent catheterization between May 28, 2011 and January 14, 2013 and were enrolled at eight sites. All sixteen patients met the study eligibility criteria and were treated with the Bare CP Stent. Table 30 documents the patient accountability for the COAST CAP.

Table 30. Patient Accountability (COAST CAP)

	Possible N (100%)	1 Month Visit n (%)	12 Month Visit n (%)	24 Month Visit n (%)
Safety Cohort	16	15	13	8
Effectiveness Cohort	16	15	13	8

The small number of patients at the 24-month time point mostly represents those who have yet to go through their 2-year window. Data collection is ongoing for the follow-up visits beyond 24 months, namely at 3, 4 and 5 years.

COAST II CAP

Forty-five patients underwent catheterizations between April 11, 2012 and August 16, 2013. Table 31 documents the patient accountability for the COAST II CAP.

Table 31. Patient Accountability (COAST II CAP)

	Possible N (100%)	1 Month Visit n (%)	12 Month Visit n (%)	24 Month Visit n (%)
Safety Cohort	45	45	40	16
Effectiveness Cohort	45	45	40	16

As noted for the COAST CAP, the small number of patients at the 24 month time point mostly represents those who have yet to go through their 2 year window. Data collection is ongoing for the follow-up visits beyond 24 months, namely at 3, 4 and 5 years.

C. Study Population Demographics and Baseline Parameters

COAST CAP

The demographics of the COAST CAP population are shown in Table 32.

Table 32. Patient Demographics and Baseline Characteristics (COAST CAP)

	Number (Percent) or Median (Range)
	Continued Access (n=16)
Gender	
Male	12 (75%)
Female	4 (25%)
Age, years	16 (9 to 47)
Age Group, years	
7 to 13	3 (19%)
14 to 17	7 (44%)
18 to 29	2 (13%)
30 to 60	4 (25%)
Weight, kg	68 (36 to 80)
Height, cm	168 (141 to 185)
NYHA Classification	
I	12 (75%)
II	3 (19%)
III	1 (6%)
Primary Indication	
Native coarctation	9 (56%)
Recurrent coarctation	7 (44%)

COAST II CAP

The demographics of the COAST II CAP population are shown in Table 33.

Table 33. Patient Demographics and Baseline Characteristics (COAST II CAP)

	Number (Percent) or Median (Range) Continued Access (n=45)
Gender	
Male	29 (64%)
Female	16 (36%)
Age, years	21 (7 to 65)
Age Group, years	
<10	3 (7%)
10 to 13	5 (11%)
14 to 17	9 (20%)
18 to 29	10 (22%)
30 to 60	17 (38%)
>60	1 (2%)
Weight, kg	69 (23 to 142)
Height, cm	164 (127 to 192)
Primary Indication	
Repair of aortic wall injury	19 (42%)
Prevention of aortic wall injury	26 (58%)

D. Safety and Effectiveness Results

1. Safety Endpoints

   Table 34 details the summary of data pertaining to the safety endpoints for the COAST CAP and COAST II CAP.

Table 34. COAST CAP and COAST II CAP Safety Endpoints

	Safety Endpoint	**N (Event Rate)**
COAST Primary	Serious or Somewhat Serious Adverse event attributed to the Stent or Implantation procedure within 30 days of the procedure	1 (6.3%)
Primary	Post-procedure paradoxical hypertension	0 (0%)
COAST II Primary	Serious or Somewhat Serious Adverse Events Attributed to the Stent, Implantation or Catheterization within 30 days of the procedure	3 (6.7%)
Secondary	Proportion of patients experiencing any AEs related to the device or implant procedure post 1 year (among 42 patients followed for at least 1 year)	0 (0%)

An overview of the adverse events observed in the COAST CAP and COAST II CAP is presented in Table 35 and 36.

Table 35. Summary of Adverse Events (AEs) for COAST CAP (n=16)

	Stent Related Events[1] (Rates)	**Stent, Implantation, or Catheterization Related Events[2] (Rates)**	**All Events (Rates)**
Patients with serious or non-serious event at 30 days	1 (6.3%)	6 (37.5%)	8 (50%)
Patients with adverse event at 12 Months	3 (18.8%)	7 (43.8%)	9 (56.3%)
Serious or somewhat serious event at 12 months	2 (12.5%)	3 (18.8%)	4 (25.0%)
Serious or somewhat serious event, excluding stent fracture at 12 months	0 (0.0%)	1 (6.3%)	3 (18.8%)
Serious event at 12 months	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Includes events that are due to or possible due to stent, and stent fractures.
[2]Includes events that are due to or possible due to stent, implantation, or catheterization, and stent fractures

Table 36. Summary of Adverse Events (AEs) for COAST II CAP (n=45)

	Stent Related Events[1] (Rates)	**Stent, Implantation, or Catheterization Related Events [2] (Rates)**	**All Events (Rates)**
Patients with serious or non-serious event at 30 days	4 (8.9%)	18 (40%)	25 (55.6%)
Patients with adverse event at 12 Months	4 (4.9%)	30 (36.6%)	58 (70.7%)
Serious or somewhat serious event at 12 months	3 (3.7%)	7 (8.5%)	14 (17.1%)
Serious or somewhat serious event, excluding stent fracture at 12 months	3 (3.7%)	7 (8.5%)	14 (17.1%)
Serious event at 12 months	1 (1.2%)	1 (1.2%)	4 (4.9%)

[1]Includes events that are due to or possible due to stent, and stent fractures.
[2]Includes events that are due to or possible due to stent, implantation, or catheterization, and stent fractures

Tables 37 and 38 document the stent related, implantation related, and catheterization related events for the COAST CAP and COAST II CAP.

Table 37: COAST CAP Stent, Implantation and Catheterization Related Events

	Number of Events (Rates)
Stent Related Events	
Expired Stent	1 (6.3%)
Increased blood pressure	1 (6.3%)
Implantation Related Events	
Back Pain	1 (6.3%)
Hematoma at access site	1 (6.3%)
Right leg pain from access site	1 (6.3%)
Catheterization Related Events	
Fever	1 (6.3%)
Headache	1 (6.3%)
Hypertension	1 (6.3%)

Table 38: COAST II CAP Stent, Implantation and Catheterization Related Events

	Number of Events (Rates)
Stent Related Events	
Chest Pain	3 (6.7%)
Stent Malposition	1 (2.2%)
Implantation Related Events	
Abdominal Pain	1 (2.2%)
Back Pain	3 (6.7%)
Chest Pain	7 (15.6%)
Groin Pain	2 (4.4%)
Lung Collapse	1 (2.2%)
Neck Pain	1 (2.2%)
Stent Migration	1 (2.2%)
Catheterization Related Events	
Blood loss from procedure	1 (2.2%)
Emesis	1 (2.2%)
Headache	1 (2.2%)
Leg pain	1 (2.2%)
Local hematoma groin	3 (6.7%)
Nausea/vomiting	1 (2.2%)
Prolonged wound healing	1 (2.2%)
Pulmonary embolism	1 (2.2%)
Re-bleed at catheterization site	1 (2.2%)

No patient in the COAST CAP cohort experienced post-procedural paradoxical hypertension. Also, no aortic wall injury was detected at 12-month follow-up. No patient in this cohort experienced a major stent malposition and no coarctation-related reinterventions were reported by 12-month follow-up. Two events were documented for non-coarctation related reintervention at 12-month follow-up, representing 12.5% of the cohort. One was a surgical intervention and one was a catheter reintervention.

Under the COAST II CAP, one patient experienced major stent malposition, which represented 2.2% of the cohort. Six patients experienced post-procedural paradoxical hypertension, representing 13.3% of the population. Of the 19 patients assessed at the 12-month follow-up, eight patients did not have wall injury and eleven did not have a baseline aortic wall injury (AWI). At 12-month follow up, four coarctation-related reintervention events were documented, representing 8.9% of the cohort. These were all catheter reinterventions. No patients had non-coarctation related reintervention by 12 month follow-up.

Two stent fractures were observed in the COAST CAP, representing 16.7% of the subjects. There was loss of structural integrity in one patient. One stent fracture was observed in the COAST II CAP, which did not result in loss of structural integrity.

2. Effectiveness Endpoints

The summary of COAST CAP and COAST II CAP effectiveness data is provided in Table 39.

Table 39. Summary of Effectiveness Data for COAST CAP and COAST II CAP

COAST CAP (N=16) ***Primary***	**Effectiveness Endpoint**	**Outcome**
	Mean Reduction in Systolic Blood Pressure Difference, Pre-Stent to the 12 Month Post-Procedure Follow-Up	21 ±23 mmHg
	Length of Stay in Hospital	1.3 ± 0.7 days
COAST II (N=45) ***Primary***	Severity of Illness Scale Grade 4 or 5 with No Clinical Worsening at 12 Month Follow-up	80%
Secondary	Proportion of patients with arm-leg systolic blood pressure differences less than 20mmHg and less than 15 mmHg at 12 month follow-up, compared to baseline	Less than 20 mmHg: 95% (up from 56% at baseline) Less than 15 mmHg: 95% (up from 35% at baseline)
	Mean reduction of upper extremity blood pressure at 1 year compared to baseline	13 ± 20mmHg95% confidence interval
	Complete repair of aortic wall defect with first Covered CP Stent (no residual endoleak during the catheterization procedure) (N=19)	17 (89%)
	Proportion of patients with effective treatment of AWI with no residual aneurysm seen on MRI scanning by 12 months follow up (N=8)	8 (100%)
	Hospital length of stay compared to length of stay for surgical repair of aortic coarctation	1.3 ± 1.2 days

The safety and effectiveness results for the COAST CAP and COAST II CAP are consistent with the results observed in the pivotal data sets.

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 Device 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. Effectiveness Conclusions

The assessment of effectiveness for the COAST trial was based on the evaluation of reduction in the systolic blood pressure (SBP) gradient (arm-leg systolic blood pressure gradient) and length of hospital stay. The results from the COAST trial did not meet the performance goal (36 mmHg) for the reduction in arm-leg SBP gradient difference (observed SBP gradient difference 31 mmHg in COAST). However, careful analysis of the data did show that COAST patients achieved complete obliteration of the pre-procedural blood pressure gradient, suggesting that failure to meet the endpoint was a function of the chosen performance goal derived from a historical cohort rather than ineffective treatment. In addition, 94 of 98 patients for whom 12- or 24-month follow-up blood pressure data are available demonstrated persistent reduction in arm-leg blood pressure difference. Approximately 93% (91/98) of patients have lower upper extremity blood pressure at 12 or 24 months compared to baseline. Furthermore, the results from the COAST trial demonstrate that the length of hospital stay is significantly less in patients who received the bare CP Stent. The average hospital stay for surgery was 3.5 days, while the stay associated with the CP Stent implantation was 1.1 days.

The assessment of effectiveness for the COAST II trial was based on improvement in aortic wall injury and/or aortic arch obstruction based on level of severity as well as evaluation of aortic wall injury and/or aortic arch obstruction at Grade 4 or above at 12 months with no clinical worsening. The results of the COAST II study indicated an improvement in clinical status relative to baseline with a median change in the Severity of Illness Scale of 2. Of the 67 patients followed to 24 months only 5 (7%) experienced any clinical worsening using the COAST II three tier, Severity of Illness Scale. All patients derived initial benefit from their implants and by 24 months 93% had shown either no change or improvement in their Severity of Illness grade compared to baseline.

B. Safety Conclusions

The safety assessment is based on non-clinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The results from the non-clinical laboratory and animal studies performed on the CP Stent and Covered CP Stent Systems demonstrate that this device is suitable for long-term implant. The safety assessments for the COAST and COAST II trials were based on the occurrence of any serious or somewhat serious adverse events. The COAST trial also included an evaluation of post-procedure paradoxical hypertension. The results from the COAST trial demonstrate that the bare CP Stent reduces the proportion of patients with serious and somewhat serious adverse events when compared to surgical intervention. The PG was also met for the reduction in the proportion of patients with post-procedure paradoxical hypertension (PPPH) compared to surgical patients. The COAST II trial results demonstrated that the Covered CP Stent reduces the proportion of patients with a serious or somewhat

serious adverse event attributed to the stent or procedure compared to surgery. There were no uncontained aortic tears, or large aneurysms or pseudo-aneurysms and all new aortic wall injuries were successfully repaired by covered stent implantation.

C. Benefit-Risk Conclusions

The risks associated with the CP Stents and Covered CP Stents include complications such as stent migration, stent fracture, vessel tear, hematoma, thrombosis, stent stenosis, aneurysm, bleeding, and death.

The probable benefits of the CP Stent and Covered CP Stent include reduction in the systolic blood pressure (SBP) gradient (arm-leg systolic blood pressure gradient) and length of hospital stay as well as reduction in post-procedural paradoxical hypertension in patients receiving the CP stent and improvement in aortic wall injury and/or aortic arch obstruction in patients receiving the Covered CP Stent.

In conclusion, given the available information above, the data support that for implantation in the native and/or recurrent coarctation of the aorta using the CP Stent or Covered CP Stent, 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. Preclinical and clinical studies provided in the PMA application demonstrate reasonable assurance that the CP Stent and CP Covered Stent, mounted or unmounted, are safe and effective for implantation in the treatment of native and/or recurrent coarctation of the aorta.

XIV. CDRH DECISION

CDRH issued an approval order on March 25, 2016. The final conditions of approval cited in the approval order are described below.

1. *ODE Lead PMA Post-Approval Study - Continued Follow-up of Premarket Cohorts:* The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study should include patients in the COAST, COAST II, COAST CAP and COAST II CAP studies who were presented as part of the PMA application dataset and alive. The study will be conducted per revision 4.0 of the COAST/COAST CAP protocol and revision 2.0 COAST II/COAST II CAP protocol. The objective of this study is to evaluate the long-term safety and effectiveness of the CP stents and Covered CP Stents through five years post-implant.

   For all COAST, COAST CAP, COAST II, and COAST II CAP patients, outcomes specified in the protocols will be reported annually, including the following:

a. Blood pressure outcomes:
    i. Percent of patients with:
        1. Systolic blood pressure (SBP) arm-leg differences under 20, 15 and 10 mmHg;
        2. Average arm–leg SBP difference; and
        3. Proportion of patients with hypertension.

b. Aortic Wall Injury (AWI) Outcomes:
    i. Clinical summaries for any patient with new or progressive AWI requiring follow-up imaging, intervention or surgery (imaging performed on a clinical basis – descriptive summary only); and
    ii. Overall incidence of patients detected with new or progressive AWI (using baseline sample size as denominator).

c. Stent Fracture Outcomes:
    i. Any new or progressive stent fracture;
    ii. Total incidence of stent fracture for bare metal and covered stents (using baseline sample size as denominator);
    iii. Descriptive summaries for each stent fracture, including need for re-intervention or surgery; and
    iv. Total incidence and types of late sequelae (e.g., none, recoarctation, pseudoaneurysm, aortic perforation, etc.).

2. *ODE Lead PMA Post-Approval Study - Continued Follow-up of Premarket Cohorts with Stent Fractures:* The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study should include all currently enrolled and alive patients in the COAST and COAST II studies with stent fractures and COAST CAP and COAST II CAP studies with stent fractures who had completed 2-year follow-up at the time of PMA submission.

   The objective of this study is to evaluate the long-term safety and effectiveness of the CP Stents and Covered CP Stents in patients with stent fractures through ten years post-implant. In addition to the outcomes listed above for the *ODE Lead PMA Post-Approval Study - Continued Follow-up of Premarket Cohorts,* the follow-up for these patients will be extended for another five years, totaling ten years post-implant. After the first five years, patients will be followed annually using direct patient survey, which will include the following evaluations: general state of health, hypertension medication usage, need for cardiac catheterization and need for cardiac surgery. Individual summaries for any patient requiring reintervention or surgery should be provided.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.