SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Renal Stent (NIN)
Device Trade Name:	RX Herculink Elite® Renal Stent System
Applicant's Name and Address:	Abbott Vascular 3200 Lakeside Drive Santa Clara, CA 95054
Date of Panel Recommendation:	Not applicable
Premarket Approval (PMA) Application Number:	P110001
Date of Notice of Approval to Applicant:	July 20, 2011
Expedited:	Not Applicable

II. INDICATIONS FOR USE

The RX Herculink Elite Renal Stent System is indicated for use in patients with atherosclerotic disease of the renal arteries following sub-optimal percutaneous transluminal renal angioplasty (PTRA) of a *de novo* or restenotic atherosclerotic lesion (≤ 15 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 - 7.0 mm. Suboptimal PTRA is defined as ≥ 50% residual stenosis, ≥ 20 mmHg peak systolic or ≥ 10 mmHg mean translesional pressure gradient, flow-limiting dissection, or TIMI [Thrombolysis In Myocardial Infarction] flow < 3.

III. CONTRAINDICATIONS

The RX Herculink Elite Renal Stent System is contraindicated for use in:

- Patients with a contraindication for antiplatelet/anticoagulant therapy.
- Patients who have a lesion that cannot be crossed with a wire or a balloon angioplasty catheter.
- Patients with bleeding disorders.
- Patients with a known hypersensitivity to cobalt or chrome.
- Target lesions that are resistant to complete balloon inflation.
- Stenting of an arterial vessel where leakage from the artery could be exacerbated by placement of a stent.

- Patients with a target lesion with a large amount of adjacent acute or subacute thrombus

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the RX Herculink Elite Renal Stent System labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The RX Herculink Elite Renal Stent System is a balloon-expandable stent, composed of L605 Cobalt Chromium, pre-mounted onto a rapid exchange (RX) delivery catheter. The stent design is based upon a series of zig-zagging rings with multiple links per ring. The stents are manufactured in two stent designs (small and large). The small stent is available in 4.0 – 6.0 mm diameters; the large stent is available in 6.5 and 7.0 mm diameters. Both stent designs comprise a series of rings with multiple links aligned along a longitudinal axis. The stent is supplied in the lengths and inner diameters described in Table 1. Table 2 contains a list of the model numbers associated with the respective device sizes.

Table 1: Dimensions of RX Herculink Elite Stents

	Length		
Diameter	**12 mm**	**15 mm**	**18 mm**
4.0 mm	X	X	X
4.5 mm	X	X	X
5.0 mm	X	X	X
5.5 mm	X	X	X
6.0 mm	X	X	X
6.5 mm	X	X	X
7.0 mm		X	X

The delivery system is a rapid exchange co-axial design with a balloon at the distal end. The delivery system for the 12 mm, 15 mm and 18 mm stent lengths is available in lengths of 80 cm and 135 cm. The delivery systems for the 12 mm, 15 mm and 18mm stent lengths differ primarily in the balloon working lengths, which are 15 mm, 18 mm and 20 mm, respectively. The crossing profile for the delivery system is ≤ 0.067" for all stent sizes. The proximal lumen provides for inflation of the balloon with contrast medium. The central distal lumen permits use of a guide wire to facilitate advancement of the catheter to and through the lesion to be dilated.

Two radiopaque markers, located underneath the balloon, identify the stent position and fluoroscopically mark the working length of the balloon to aid in positioning the stent within the lesion. The balloon is designed to provide an expandable segment of known diameter and length at specified pressures. It has a rated burst pressure of 14 atm.

Markers located on the proximal outer shaft help the physician gauge the catheter position relative to the guiding catheter tip. An adaptation arm on the proximal end of the delivery system provides access to the inflation lumen. It is designed with a luer-lock fitting for connection with an inflation device.

Table 2: RX Herculink Elite Renal Stent System Model Numbers

Stent Diameter (mm)	Catheter Length = 80 cm Stent Length			Catheter Length = 135 cm Stent Length		
	12 mm	15 mm	18 mm	12 mm	15 mm	18 mm
4.0	1011486-12	1011486-15	1011486-18	1011487-12	1011487-15	1011487-18
4.5	1011489-12	1011489-15	1011489-18	1011490-12	1011490-15	1011490-18
5.0	1011492-12	1011492-15	1011492-18	1011493-12	1011493-15	1011493-18
5.5	1011495-12	1011495-15	1011495-18	1011496-12	1011496-15	1011496-18
6.0	1011498-12	1011498-15	1011498-18	1011499-12	1011499-15	1011499-18
6.5	1011501-12	1011501-15	1011501-18	1011502-12	1011502-15	1011502-18
7.0		1011504-15	1011504-18		1011505-15	1011505-18

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of atherosclerotic renal artery stenosis:

- Non-invasive treatment (drug therapy)
- Minimally invasive treatment (balloon angioplasty, endovascular stent placement using a different renal stent system, or atherectomy)
- Surgical treatment (aorto-renal bypass)

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 Herculink Elite has been commercially available in the United States as a biliary stent since March 6, 2006. In addition, the same device named the RX Herculink Elite

Peripheral Stent System is commercially available in over 80 countries outside the United States.

The Herculink Elite has not been withdrawn from marketing in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with the use of a renal stent include, but are not limited to:

- Abscess
- Allergic reaction to Cobalt Chromium or contrast agents
- Arrhythmias (ventricular fibrillation, ventricular tachycardia, other)
- Arteriovenous fistula
- Bowel infarct
- Death
- Dialysis
- Dissection
- Drug reaction to antiplatelet agents
- Drug reaction, allergic reaction to contrast media
- Emboli (air, tissue, or thrombotic emboli) resulting in tissue ischemia/infarction
- Emergency surgery to correct vascular complications
- Emergent renal artery bypass surgery
- Extremity ischemia/amputation
- Fever
- Gastrointestinal symptoms from anticoagulation/antiplatelet medication
- Hematoma at vascular access site
- Hemorrhage requiring transfusion
- Hypersensitivity reactions
- Hypotension/hypertension
- Infection and pain at vascular access site
- Intimal tear
- Kidney infarct
- Myocardial infarction
- Myocardial ischemia
- Nephrectomy
- Peripheral neuropathy
- Pseudoaneurysm at vascular access site
- Pseudoaneurysm formation
- Renal artery thrombosis, aneurysm, rupture, perforation, occlusion, spasm, or restenosis
- Renal insufficiency or failure
- Stent migration or embolization
- Stent misplacement
- Stroke/cerebral vascular accident

- Tissue necrosis or ulceration

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

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies related to the RX Herculink Elite Renal Stent System were performed. Studies included those performed on the stent, the delivery system, or the entire device (stent mounted on delivery system).

A. Biocompatibility

A thorough panel of biocompatibility testing was performed on the Herculink Elite stent and delivery system in accordance with FDA's Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, ISO 10993: Biological Evaluation of Medical Devices, and 21 CFR § 58 Good Laboratory Practice (GLP) requirements. The stent was assessed by tests considered appropriate for a permanent (> 30 days) blood-contacting implant, and the delivery systems were assessed by tests considered appropriate for a limited time, circulating-blood-contacting, externally-communicating device.

Table 3 summarizes the biocompatibility test results. The test results show that all patient- and fluid-path-contact materials for the stent and both delivery systems met the acceptance criteria for the tests, which FDA believed were appropriate; therefore, the results support the safety of the RX Herculink Elite Renal Stent System for clinical use.

Table 3: Biocompatibility Testing Summary for the RX Herculink Elite Renal Stent System

Biocompatibility Test	Test Article	Purpose	Acceptance Criteria	Result
Cytotoxicity, MEM Elution ISO 10993-5: 2009	Stent and delivery systems	To determine the potential for cytotoxicity.	The sample is considered non-cytotoxic if the grade assigned from the Cytotoxicity Scale is less than or equal to grade 2 (mild).	Pass
Sensitization, Guinea Pig Maximization ISO 10993-10: 2002 & A1:2006	Stent and delivery systems	To evaluate the potential for delayed dermal contact sensitization.	Skin reaction scores received by the test group which are greater than the scores received by the negative control group, are considered to represent significant sensitization.	Pass

Table 3: Biocompatibility Testing Summary for the RX Herculink Elite Renal Stent System

Biocompatibility Test	Test Article	Purpose	Acceptance Criteria	Result
Irritation, Intracutaneous Toxicity ISO 10993-10: 2002 & A1:2006	Stent and delivery systems	To assess possible contact hazards from chemicals released from medical devices that may produce skin and mucosal irritation, eye irritation and delayed contact hypersensitivity.	The requirements of the test are met if the difference between the mean score for the sample extract and the mean score for the corresponding blank is 1.0 or less (negligible or slight)	Pass
Acute Systemic Toxicity ISO 10993-11: 2009	Stent and delivery systems	To determine the potential for systemic toxicity.	The requirements of the test are met if none of the animals treated with the sample extract show a significantly greater biological reactivity than the control animals. No significant biological activation over 72 hours	Pass
Material-Mediated Pyrogenicity ISO 10993-11: 2009	Stent	To determine whether an extract of the test article induced a pyrogenic response following injection in rabbits.	If no rabbit shows an individual rise in temperature of 0.5°C or more above its respective control temperature, the test article meets the requirements for the absence of pyrogens.	Pass
Hemocompatibility, Complement Activation C3a ISO 10993-4: 2002	Stent and delivery system	To evaluate the evidence of irritation or toxicity at 4 weeks.	Characterization only for non-compendial tests	N/A
Hemocompatibility, Complement Activation SC5b-9 ISO 10993-4: 2002	Stent and delivery system	To evaluate the evidence of irritation or toxicity at 12 weeks.	Characterization only for non-compendial tests	N/A
In Vitro Hemolysis Study (Modified ASTM Extraction Method)	Stent and delivery systems	To determine whether the presence of any leachable chemicals from the test article would cause *in vitro* red blood cell hemolysis.	0-2% hemolytic index	Pass

Tests for subchronic toxicity, chronic toxicity, genotoxicity, carcinogenicity, *in vivo* thrombogenicity, and muscle implantation were not performed due to the extensive clinical history of the device materials and their well-characterized long-term safety profile. Thrombogenicity was also assessed in the 3-, 28- and 180-day animal studies.

B. Animal Studies

Three separate animal studies were successfully conducted using the RX Herculink Elite Stent System. An *in vivo* acute animal study was conducted to demonstrate whether

functionality and usage of the RX Herculink Elite Stent System, in both the single and overlapped configuration, were clinically acceptable in the physiological environment when tested in healthy porcine arteries. A GLP animal study was conducted to evaluate the vascular response of the RX Herculink Elite Stent System in the peripheral vasculature of Swine (3-day and 28-day). Finally, a 180-day *in vivo* animal study of the RX Herculink Elite Stent System was conducted in the porcine renal artery to evaluate the effects of stent implantation on the renal artery and downstream effects on the kidney.

Table 4: Animal Testing Summary for the RX Herculink Renal Stent System

Study Objectives	Number of Animals Timepoints Devices Tested	Relevant Findings
Acute Performance of RX Herculink Elite Stent System in Porcine Renal Arteries		
Evaluate the acute functional performance of the RX Herculink Elite Stent System in the healthy swine model that simulates the clinical application of the renal system.	• 2 animals • Acute response • 15 Herculink Elite stents • 4 Herculink Plus stents	• Device successfully delivered and deployed stents to all target implant sites in both swine. • No vessel anomalies were observed at pre- or post-implant angiograms. • No vessel injury was observed at post implant angiograms. • All attributes of the performance evaluation were rated as "PASS." • The performance of modified RX Herculink Elite Stent System was comparable to that of currently marketed RX Herculink Plus Stent System in all of the relevant attributes, except in one development the modified RX Herculink® Elite TM Stent System performed better in the smooth guidewire movement than the RX Herculink Plus Stent System. • Two Herculink Elite stents were overlapped in the carotid artery of each animal without complications (approximately 50% overlap).
3-day and 28-day GLP Study to Evaluate the Vascular Response of the RX Herculink Elite Stent System in Peripheral Vasculature of Swine		

Table 4: Animal Testing Summary for the RX Herculink Renal Stent System

Study Objectives	Number of Animals Timepoints Devices Tested	Relevant Findings
To evaluate the vascular response to the RX Herculink Elite Stent System in the renal vascular anatomy of normal swine at day 3 and day 28 time points.	• 7 animals • 6 stents of 4.0 mm, 6 stents of 6.0 mm and 9 stents of 7.0 mm, with 3 pairs of overlapping stents were implanted for 3-day time point. • For 28-day time point, implanted 9 stents of 4.0 mm, 1 stent of 5.0 mm, 10 stents of 6.0 mm and 8 stents of 7.0 mm, with 4 pairs of overlapping stents.	• No animal deaths through 28 days. • No dissection. • Angiography revealed normal blood flow. • No aneurysms. • No acute thrombus. • Stent struts apposed to vessel wall. • No distal embolization observed. • Vessel injury was very mild (mean injury score by the Schwartz grading system' of 0.97±0.17 at Day 3 and 1.07±0.42 at day 28). • No outer diameter enlargement (arterial diameter), no medial thinning (medial area) and no protrusion of the stent into the vessel lumen were observed. • At the day 28 time point, mean percent diameter stenosis was 4.77 ± 5.90%
Long Term *In Vivo* Study of the RX Herculink Elite Stent System Implanted in Porcine Renal Artery for 180-Days		
To evaluate the effects of stent implantation on the renal artery and downstream effects on the kidney (i.e. thrombi and lesions) in comparison with the kidney on unstented renal artery side by angiographic and histopathologic analyses.	• 8 animals • 181 days • 8 Herculink Elite stents	• All animals survived to endpoint. • No stent migration. • Complete perfusion of arteries. • No filling defects or dissections. • Some stent struts not well apposed. However, complete stent integrity with no strut breaks. • Stented segments had low mean injury and inflammation scores, with 2 animals having higher scores. • No significant difference was noted between kidneys located downstream of stented and non-stented arteries. • Low intimal hyperplasia.

The animal studies demonstrated that the stents did not cause any abnormal localized tissue responses and the delivery systems were tracked, the stents deployed, and the delivery systems withdrawn without difficulty or incident. Moreover, the results showed no safety problems associated with the stents. The performance testing of the RX Herculink Elite Stent System demonstrated adequate functional performance. Therefore, the animal testing results for the RX Herculink Elite Stent System support a reasonable assurance of device safety and effectiveness.

C. In-Vitro Bench Testing

Comprehensive *in vitro* laboratory testing was performed on the RX Herculink Elite Renal Stent System to verify that the performance attributes are sufficient for the device to perform as intended and to minimize the risk of adverse events under anticipated clinical conditions. This test plan was developed in accordance with FDA's *Guidance for Industry and FDA Staff: Non-clinical tests and recommended labeling for intravascular stents and associated delivery systems* (April 18, 2010). Table 5 summarizes the *in vitro* laboratory testing results. The test results verified that the RX Herculink stent and delivery system met their product performance and design specifications and would perform as intended under anticipated clinical conditions.

Table 5: In Vitro Laboratory Testing Summary for the RX Herculink Elite Renal Stent System

Type of Study	Objective	Summary of Method and Result
Pitting and Crevice Corrosion: Single Stent / Bending Fatigue & Overlapped / Radial Fatigue	To document the potential for pitting and crevice corrosion of the stent.	Cyclic potentiodynamic polarization testing was performed to determined breakdown potential of the stent. All five tested specimens did not have a breakdown potential below 800 mV with respect to Saturated Calomel Electrode (SCE).
Dimensional Verification	To characterize the dimension of the stent	Various measurements were taken on stents after deployment from the balloon catheters. The diameter and length of the stents were within ± 10% of labeled length and diameter. The maximum and minimum outer diameter along the stents varied < 0.5 mm.
Unexpanded Stent/Crimp Stent Diameter/Crossing Profile	To determine the maximum diameter found between the proximal end of the mounted stent and the distal tip of the delivery system.	The crossing profile was measured to assure a crossing profile of ≤ 0.067".
Uniformity of Expansion	To determine the difference between largest and smallest stent outside diameter (OD) along the stent length.	Stent was inflated to nominal pressure to assure uniformity within 0.8 mm.
Foreshortening (Minimum Expanded Stent Length)	To determine the stent length change before deployment and after deployment.	Unexpanded stent length was measured, stent was deployed, then deployed length was measured. Maximum foreshortening for all stents was 8.4%,.
Recoil for Balloon Expandable Stents	To determine the change in stent diameter after balloon expansion and after balloon deflation.	Stent OD measured with and without balloon inflated to nominal pressure. Maximum recoil was 6%.
Radial Stiffness and Radial Strength	To determine the radial strength of the RX Herculink Elite.	Stent was deployed inside a precision expansion block to measure circumferential radial strength. Minimum radial strength was 1096 mmHg. Minimum radial stiffness was 1.81 mmHg/micron.

Table 5: In Vitro Laboratory Testing Summary for the RX Herculink Elite Renal Stent System

Type of Study	Objective	Summary of Method and Result
Mechanical Properties	To characterize the stent material for the purpose of developing parameters for a finite element analysis of the stent	Ultimate tensile strength was determined on the raw stent material via standard tensile testing equipment. The ultimate tensile strength was 165 ksi.
Stent Integrity	To provide assurance that the stent has no clinically significant cracks or flaws after expansion or (as a worst case) an intentional balloon rupture	The stent is expanded through balloon inflation to the maximum labeled pressure (17atm) and then visually inspected for fractures. Examination under magnification detected no clinically significant cracks or flaws.
Accelerated Bending Fatigue	The purpose of this testing was to evaluate the 10-year real time equivalent of single stent bending fatigue resistance of Herculink Elite stents. The stents were subjected to worst-case bending conditions anticipated in the renal arteries.	Tests were run for 80 million cycles, with stents then examined for fractures. No stents had Type II fracture (as defined by Rocha-Singh et al.[1]); three stents with Type I fracture showed no detachment of any part of the stent.
Accelerated Radial Fatigue	The purpose of this test was to evaluate the long-term fatigue resistance (10 years real-time equivalent) of the Herculink Elite stent in an overlapped state in a physiologically simulated environment with accelerated dynamic radial loading.	Stents subjected to 400 million cycles of radial fatigue and then examined for fractures. No stents had Type II or Type I fracture (as defined by Rocha-Singh et al.[1]).
Magnetic Resonance Imaging	Testing and analysis were performed to determine the parameters for which patients with the Herculink Elite will not be subjected to added risk during MRI.	Measured device response to MR fields at 64 MHz (1.5T) and at 128 MHz (3T). Both small and large stent designs were tested and results allow an MR Conditional rating at 3 Tesla.
Radiopacity	The purpose of this test was to assess the radiopacity of the RX Herculink Elite Stent System in a simulated clinical setting.	The stent and delivery system were assessed as having good to excellent radiopacity in various *in vivo* renal artery models.
Delivery System Dimensional Verification	Dimensional measurements were taken and compared with the product specification.	All dimensional verification tests passed the acceptance criteria
Delivery, Deployment, Retraction, Coating Integrity	To assess the performance of the device in a simulated clinical setting. This testing evaluated functional attributes by assessing the clinical acceptability of delivery, deployment, retraction and coating integrity of the device.	Herculink Elite Renal Stent System was tracked through a validated multi-renal artery model, an *in vitro* model that mimics the *in vivo* physiologic and anatomic conditions and morphology found in human patients with renal artery disease. All test articles passed.
Balloon Rated Burst Pressure (RBP)	To determine the pressure at which 99.9% of balloons can survive with 95% confidence.	Inflate balloon until balloon is ruptured. Minimum pressure was 256 psi.

Table 5: In Vitro Laboratory Testing Summary for the RX Herculink Elite Renal Stent System

Type of Study	Objective	Summary of Method and Result
Balloon Fatigue	To determine the ability of the balloon to withstand repeated inflation cycles to RBP.	Performed ten (10) fatigue cycles. All sizes met the acceptance criteria.
Balloon Compliance/Stent OD	To determine the stent OD at various pressures	Inflate balloon until balloon ruptured. Stent OD was measured at each incremental pressure. All stents were nominal diameter at nominal pressure.
Balloon Inflation/Deflation	To determine the balloon inflation and deflation times.	Measured the time it takes to inflate / deflate the balloon to and from rated burst pressure. The maximum inflation time was 1 seconds; the maximum deflation time was 12 seconds.
Catheter Bond Strength	To determine the strength of the catheter bonds.	Individual bonds were pulled on a tensile tester until failure. All bond strengths were greater than the acceptance criteria.
Flexibility and Kink Test	To determine the kinking of the RX Herculink Elite.	Catheter was inserted into kink test fixture and subjected to bend radii < 11 mm. There were no device failures.
Torque Strength	To determine the torque strength of the device.	Tip was locked in fixture and catheter was rotated until failure. Minimum number of rotations before failure was 5.
Stent Movement	To determine the distance the stent moves after being tracked through a tortuous path fixture.	Catheter was inserted through a conditioning fixture two times. No stent moved by more than 2 mm from its original position on the balloon.
Stent Dislodgement	To determine the force required to dislodge the crimped stent.	Catheter inserted through a preconditioning fixture twice. Minimum dislodgement force was 0.8 lbs.

[1]Rocha-Singh, et al. *Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients With Symptomatic Peripheral Arterial Disease.* Catheterization and Cardiovascular Interventions. 69: 910-919.

In vitro bench testing was performed to assess the functional characteristics of the RX Herculink Elite Renal Stent System. The results indicate that the device adequately satisfied the relevant FDA reliability guidelines as outlined in *Guidance for Industry and FDA Staff – Non-clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* (April 18, 2010). In addition, the accelerated aging test results indicate that the RX Herculink Elite Renal Stent System will maintain functional characteristics for the current shelf life of 16 months. The acceptance criteria were met for each of the above tests.

D. Sterilization, Packaging and Shelf-Life

In accordance with ANSI/AAMI/ISO 11137-1:2006, *Sterilization of Health Care Products – Radiation – Part 1: Requirements for Development, Validation and Routine*

Control of a Sterilization Process for Medical Devices, the RX Herculink Elite Renal Stent System is sterilized by e-beam radiation to achieve a minimal sterility assurance level (SAL) of 10^{-6}. Product and package stability testing on the RX Herculink Elite Renal Stent System was performed and validated for up to a three-year shelf life per accelerated aging tests.

X. SUMMARY OF CLINICAL STUDIES

Results from a multi-center clinical study (IDE G060067, also known as the HERCULES study) demonstrate the safety and effectiveness of the RX Herculink Elite Renal Stent System. Specifically, the 9-month binary restenosis rate was 10.5%, meeting the performance goal of 28.6%. In addition, use of the RX Herculink Elite Renal Stent System was associated with a low rate of major adverse events (MAEs), high technical and procedural success rates, improvement in hypertension, and maintenance of renal function.

An overview of the HERCULES study is presented in Table 6.

Table 6: Overview of the HERCULES study

Device	RX Herculink Elite Renal Stent System
Study Design	Non-randomized, prospective, single-arm, multi-center clinical study
Patients Enrolled	202 (76 male and 126 female)
Number of Sites	37 investigational sites
Primary Endpoint	Binary restenosis rate at 9 months, defined as ≥ 60% diameter stenosis, measured by duplex ultrasound (or quantitative angiography, if necessary) by an independent core laboratory. Analysis was done on a per-lesion basis.
Secondary Endpoints	MAEs: A composite safety endpoint of the following indices: death for any reason at 30 days; ipsilateral nephrectomy at 30 days; embolic events resulting in kidney damage at 30 days; and clinically indicated target lesion revascularization (TLR) up to 9 months (270 days). Change in blood pressure: Systolic and diastolic blood pressures were measured at baseline, post-procedure, 1, 6 and 9 months and the group average at each time point reported. The change at 9 months from baseline, for systolic and diastolic pressure, was calculated for each enrolled patient. Confidence intervals (95%) for the average changes were reported. In addition, systolic blood pressure was reported using categories of < 140 mmHg, ≥ 140 mmHg and < 160 mmHg, ≥ 160 mmHg and < 180 mmHg, and ≥ 180 mmHg. Change in Antihypertensive Medications: Number and type of antihypertensive medications at baseline, 1, 6, and 9 months were collected. The group average number of antihypertensive medications at each time point was reported. In addition, data was reported as a percentage of patients on 1, 2, 3, or 4 or more medications at baseline, 1, 6, and 9 months. Change in Renal Function: Defined as change in serum creatinine (sCr), it was measured at baseline, post-procedure, 1, 6 and 9 months, with the group average

Table 6: Overview of the HERCULES study

	reported at each time point. The change at 9 months from baseline was calculated for each enrolled patient. Acute Device Success: The achievement of successful delivery and deployment of the assigned device(s) and successful removal of the delivery system as intended to the designated location. It was reported as a percentage of devices that were attempted to be implanted. Acute Clinical Success: procedure success without major adverse events (MAE) or access site events requiring surgical or percutaneous intervention prior to hospital discharge. It is presented on a per subject basis. Clinically Indicated Target Lesion Revascularization: Defined as diameter stenosis ≥ 60%, as determined by the angiographic or ultrasound core laboratory, and any revascularization (including but not limited to atherectomy, embolectomy, endarterectomy, bypass surgery, repeat angioplasty, or stent implantation) to the target lesion. Freedom from clinically indicated TLR was evaluated at 9 months and is presented as time to first event on a per-lesion basis. Acute Procedural Success: The attainment of a final result of < 30% residual stenosis as determined by the angiographic core laboratory, reported as a percentage of treated lesions.
Study Hypothesis	Renal arteries treated with the RX Herculink Elite Stent will have a binary restenosis rate at 9 months that meets a performance goal of 28.6%.
Patient Follow-up	1-month clinic visit: Blood pressure measurement, anti-hypertensive medication review, laboratory (sCr, BNP assay), duplex ultrasound, laboratory, adverse events. 6-month clinic visit: Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr). 9-month clinic visit with ultrasound: Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound, angiogram (only if duplex ultrasound done at nine-month follow up visit is determined to be "not evaluable", or at the discretion of the Investigator). 12-month clinic visit: Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr). 24-month clinic visit: Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound. 36-month clinic visit: Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.

A. Study Design

The primary objective of the clinical study was to assess the binary restenosis rate at 9 months after stenting, with binary restenosis determined by duplex ultrasound or angiogram. The lesion was considered restenotic if the lesion was ≥ 60% diameter stenosed prior to the 9-month primary endpoint evaluation. Specifically, the primary

hypothesis was that the binary restenosis rate at 9 months on a lesion basis meets the performance goal of 28.6% (i.e., < 28.6%). Secondary analyses included MAEs (defined as death for any reason at 30 days, ipsilateral nephrectomy at 30 days, clinically-indicated target lesion revascularization up to 9 months, and embolic events resulting in kidney damage at 30 days), acute device success, acute procedural success, acute clinical success, changes in blood pressures at 9 months, change in anti-hypertensive medication in-take at 9 months, and renal function outcomes (measured by serum creatinine).

The HERCULES study was a prospective, non-randomized, multi-center, single-arm clinical study to demonstrate efficacy and safety of the RX Herculink Elite Renal Stent System (Herculink Elite) in the treatment of suboptimal post-procedural percutaneous transluminal renal angioplasty (PTRA) of atherosclerotic de novo or restenotic renal artery stenoses in patients with uncontrolled hypertension. Subjects were eligible to enroll in the study if they had a suboptimal angioplasty (defined as ≥ 50% residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, flow-limiting dissection or TIMI [Thrombolysis In Myocardial Infarction] flow < 3) for *de novo* or restenotic renal artery lesions (≤ 15 mm length) due to atherosclerosis originating within 10 mm of the renal ostium, a reference vessel diameter ≥ 4 mm and ≤ 7 mm, and uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg on at least two anti-hypertensive medications). Treatment of two lesions, one per side, was allowed per patient. Patients were excluded from the study if they met any of the following conditions: only one functioning kidney, kidney transplant, had a Q-wave myocardial infarction (MI) within 30-days of the index procedure, or serum creatinine ≥ 2.5 mg/dl. Angiography was performed post stent implantation. Follow-up included ultrasound imaging at 1 month, and ultrasound (angiogram, if ultrasound was not interpretable) at 9 months. Clinical assessments (e.g., blood chemistry, blood pressure, assessment of anti-hypertensive medications) were scheduled for 1, 6, 9, 12, 24, and 36 months.

Independent core laboratories analyzed angiographic and ultrasonic imaging. The study was overseen by an independent data safety monitoring board (DSMB) comprised of physicians and a biostatistician. The committee was set up and convened at the pre-specified interim time points of the trial to evaluate the safety of the trial. A Clinical Endpoint Adjudication Committee (CEAC) adjudicated the suspected cases of peri-procedural death, ipsilateral nephrectomy and embolic events that result in kidney damage.

The principal effectiveness of the Herculink Elite was evaluated to determine if the binary restenosis rate at 9 months was less than the performance goal (PG) of 28.6% that was derived from the contemporary literature of PTRA and stenting for the atherosclerotic lesions in the aortorenal ostium. The sample size and power calculation were based on the primary endpoint of binary restenosis rate at 9 months. The PG for the binary restenosis rate at 9 months was determined to be 28.6%, based on pre-market studies of other renal artery stents used in a similar manner and which are now PMA-approved.

The primary and secondary endpoints measuring the safety and effectiveness of the device and procedure are described below.

Null Hypothesis: the 9-month binary restenosis rate, γ, is greater than or equal to 28.6%. (Interpretation: the binary restenosis rate does not meet a performance goal of 28.6%.)

Ho: $\gamma \geq 28.6\%$

Alternative Hypothesis: the 9-month binary restenosis rate, γ, is less than 28.6%. (Interpretation: the binary restenosis rate meets a performance goal of 28.6%.)

Ha: $\gamma < 28.6\%$.

The null hypothesis was tested using one-sided exact binomial test at significance level of 0.05.

For binary and categorical variables, event counts, rates and their confidence intervals were analyzed. Continuous variables were analyzed using the mean, standard deviation, and 95% confidence intervals (CI). Kaplan-Meier methodology was used to estimate the distributions of time-to-event variables.

i. Clinical Inclusion and Exclusion Criteria

The inclusion criteria for the HERCULES study were as follows:

- Subject is $\geq$ 18 years of age.
- Subject and subject's physician agree to have the subject return for all required contact following study enrollment.
- Subject has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site.
- Subject is a candidate for renal artery stenting.
- Subject has uncontrolled systolic hypertension (systolic BP $\geq$ 140 mmHg), or uncontrolled diastolic hypertension (diastolic BP $\geq$ 90 mmHg), or a combination of both in the presence of at least two (2) or more antihypertensive medications.
- Baseline sCr of $\leq$ 2.5 mg/dl.
- Subject has unilateral or bilateral *de novo* or restenotic after PTA (in-stent restenosis excluded) atherosclerotic lesion(s). If bilateral lesions are to be treated, the most severe lesion must be successfully treated without complications before progressing to treat the second lesion. Treatment of bilateral lesions is to occur in the same procedural event.
- Renal stenosis must be visually estimated to be $\geq$ 60% by angiography.
- Subject has a suboptimal PTA result, defined as one of the following:
    - $\geq$ 50% residual stenosis,
    - 10 mm Hg mean gradient or 20 mm Hg peak systolic gradient across the target lesion, or

    - A flow-limiting dissection (NHLBI grade D) or TIMI flow < 3.
- Renal stenosis must be visually estimated to be within 10 mm of the aortic renal border by angiography.
- Target vessel reference diameter must be visually estimated to be ≥ 4 mm and ≤ 7 mm by angiography.
- Target lesion length must be visually estimated to be ≤ 15 mm (including dissection) by angiography.
- Expected ability to deliver the stent to the lesion (absence of excessive tortuosity or calcification).
- Expected ability to fully expand the stent.

The exclusion criteria for the HERCULES study were as follows:

- Known hypersensitivity or contraindication to cobalt chromium or standard intraprocedure anticoagulant(s); sensitivity to contrast which cannot be adequately pre-treated with medication.
- Known allergy or contraindication to clopidogrel (Plavix) or aspirin.
- Bleeding disorder or hypercoagulable disorder, or will refuse blood transfusions.
- Gastrointestinal (GI) bleeding within 30 days before the index procedure that would interfere with antiplatelet therapy.
- Renal insufficiency, defined as serum Creatinine > 2.5 mg/dl.
- Any immunosuppressive disorder, access site infection, or acute systemic infection due to any cause.
- Medical illnesses (e.g., cancer, end-stage congestive heart failure) that may cause the subject to be non-compliant with protocol requirements, confound the data interpretation, or is associated with a life expectancy of less than three years.
- Medical illnesses that would make them unlikely to respond to treatment (e.g., sickle cell nephropathy/sickle cell disease, scleroderma, arteriolar nephrosclerosis, hemolytic-uremic syndrome and vasculitis).
- Q-wave MI within 30 days before index procedure.
- Stroke or transient ischemic attack (TIA) within 30 days before index procedure.
- History of congestive heart failure and has a previously documented left ventricular ejection fraction (LVEF) < 25%.
- Subject is normotensive or has adequate control of hypertension (SBP <140 mm Hg and DBP <90 mm Hg) utilizing diet control and/or medication regimen involving only one antihypertensive medication.
- Acute thrombophlebitis or deep vein thrombosis.
- Actively participation in another drug or device trial and did not complete the required protocol follow-up period. Subject may be enrolled only once in this study and may not participate in any other clinical trial during the follow-up period.
- Unable to understand and cooperate with study procedures or provide informed consent.
- Unable to return for follow-up visits.
- Subject is pregnant.

- Subject has undergone vascular surgery, such as coronary artery bypass grafting, abdominal aortic aneurysm repair, or aorto-femoral bypass, and has not fully recovered from the effects of surgery (<3 months).
- Subject has planned staged treatment of bilateral renal artery stenosis.
- Subject has had prior surgical intervention to the target artery, or has undergone previous stent placement in the target lesion.
- Target lesion is located in a transplanted kidney.
- Kidney to be treated is < 8 cm as determined by duplex ultrasound report, computed tomography angiography (CTA) report, or magnetic resonance angiography (MRA) report within 180 days before procedure. If kidney size is documented by more than one method, e.g. CTA and ultrasound, and one of the methods is duplex ultrasound, the kidney size as documented by duplex ultrasound shall be used to determine study eligibility.
- Subject has planned additional ancillary procedure(s) during renal stenting procedure.

Angiographic Exclusion Criteria:

- Subject has a lesion segment, including dissection, >15 mm in length.
- Requirement for more than 1 stent to treat full length of lesion and dissection.
- Target lesion has a total (100%) occlusion.
- Evidence of thrombus or mobile filling defect in the target lesion or vessel.
- Co-existing aneurysmal or occlusive disease of the abdominal aorta requiring surgical reconstruction during the follow-up period.
- Fibromuscular dysplasia.
- Subject artery has patent bifurcation within 10 mm of ostium that might be covered by placement of a stent.
- The target lesion is within the artery of a solitary functioning kidney or, the subject has a contralateral totally occluded renal artery.
- For planned treatment of bilateral lesions: the more critical lesion, i.e. lesion with the greater stenosis (which should be treated first), is either treated unsuccessfully or requires a bailout procedure. (NOTE: Less critical lesion is excluded at this point.) .

ii. Follow-up Schedule

Clinical assessments occurred at baseline, operative/discharge and postoperative intervals at 1, 6, 9 months and 1, 2, and 3 years, as seen in Table 7.

Table 7: Availability of Clinical and Imaging Follow-up Data

Follow-up Period	Clinical Evaluations
1-month clinic visit	Blood pressure measurement, anti-hypertensive medication review, laboratory (sCr, BNP assay), duplex ultrasound, laboratory, adverse events.

Table 7: Availability of Clinical and Imaging Follow-up Data

Follow-up Period	Clinical Evaluations
6-month clinic visit	Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr).
9-month clinic visit with ultrasound	Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound, angiogram (only if duplex ultrasound done at nine-month follow up visit is determined to be "not evaluable", or at the discretion of the Investigator).
12-month clinic visit	Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr)
24-month clinic visit	Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.
36-month clinic visit	Blood pressure measurement, anti-hypertensive medication review, adverse events, laboratory (sCr), duplex ultrasound.

iii. Clinical Endpoints

With regards to safety, there were no hypothesis-driven primary or secondary safety endpoints.

With regards to effectiveness, the primary effectiveness endpoint was evaluated according to the hypothesis that renal arteries treated with the RX Herculink Elite Renal Stent will have a binary restenosis rate at 9 months on a lesion basis that meets a performance goal of 28.6%. The formulation of the hypothesis can be found in Section X.A. The study was considered a success if the primary effectiveness hypothesis was met.

B. Accountability of PMA Cohort

Patient availability for study follow-up through 9 months is summarized in Table 8

The first subject was enrolled into the HERCULES study on August 31, 2007 and the last subject was enrolled on October 2, 2009. Over this period, 202 male and female subjects, who met the eligibility criteria and agreed to participate in the study and signed an informed consent, were enrolled at 37 study sites in the United States (US). Thirty-nine (39) subjects had bilateral lesions treated. Therefore, the intention-to-treat (ITT) population consists of 202 subjects and 241 lesions.

The last 9-month follow-up visit was completed on June 23, 2010. One subject did not have any post-procedure follow-up, a second subject was confirmed as lost-to-follow up at 182 days, and 4 subjects were withdrawn from the study. Through the 9 month follow-up 5 subjects expired. Three subjects had a study stent attempted without success, and a non-study stent implanted; they completed the study at the 30 day follow-up timepoint. Therefore, there were a total of 189 subjects eligible for the 9 month follow-up visit.

Table 8: Accountability of PMA Cohort

	1-month visit	6-month visit	9-month visit
Death	0	4	1
Withdrawn	0	0	4
Lost to follow-up	0	1	0
30-day follow-up complete for non-study stent	0	3	0
Eligible	**202**	**194**	**189**

C. Study Population Demographics and Baseline Parameters

Patient demographics (Table 9), medical history (Table 10), baseline blood pressure and medications (Table 11) and baseline lesion characteristics (Table 12 and Table 13) were consistent with patient populations described in published literature of renal stent intervention. The mean age of the study populations was 72.1 ± 9.4, with 62.4% female gender. The key risk factors include diabetes mellitus 45.0%, hypercholesterolemia 86.1%, coronary artery disease 67.3% and current or former tobacco use 56.9%. The baseline mean creatinine was 1.2 ± 0.4 mg/dl and 61.5% of subjects had an estimated baseline glomerular filtration rate (eGFR) of < 60 ml/min per 1.73 m^2 (Table 10).

Table 9: Patient Demographics

Demographic	Value (N = 202 patients)
Sex	
Male	37.6% (76/202)
Female	62.4% (126/202)
Age (years, mean ± SD (range))	72.1 ± 9.4 (44 - 89)
Ethnicity	
Caucasian or White	83.7% (169/202)
Black or African American	7.9% (16/202)
Hispanic or Latino	7.4% (15/202)
Other	1.0% (2/202)
Native Hawaiian or other Pacific Islander	0.5% (1/202)
Asian	0.5% (1/202)

Table 10: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Diabetes	
Total	45.0% (91/202)
Type I	3.5% (7/202)
Type II	41.6% (84/202)
Hypercholesterolemia	
Total	86.1% (174/202)
Requiring medication	82.2% (166/202)
Not Requiring medication	4.0% (8/202)
Coronary Artery Disease	67.3% (136/202)
Brain Natriuretic Peptide (BNP) Level (pg/ml)	181.2 ± 297.0 (192)
Renal Function	
Serum Creatinine (mg/dl)	1.2 ± 0.4 (202)
eGFR < 60 ml/min per 1.73 m^2	61.5% (123/200)
Former Smoker	44.1% (89/202)
Current Smoker	12.9% (26/202)

Table 11: Baseline Blood Pressure and Medications

Past or Current Medical Condition	Percent Patients (number/total number)
Blood Pressue	
Mean Systolic	162.3 ± 18.5 (202)
Mean Diastolic	77.7 ± 11.5 (202)
Anti-Hypertensive Medications	
1 Medication	0.5% (1/202)
2 Medications	29.2% (59/202)
3 Medications	30.7% (62/202)
≥ 4 Medications	39.6% (80/202)

Table 12: Baseline Lesion Characteristics

Characteristic	Percent Lesions (number/total number)
Lesion Location	
Right Renal Artery	52.3% (126/241)
Left Renal Artery	47.7% (115/241)

Table 12: Baseline Lesion Characteristics

Characteristic	Percent Lesions (number/total number)
Type of Lesion	
Restenotic	0% (0/115)
de novo	100% (241/241)
Target Lesion Location	
Ostial	67.6% (163/241)
Within 10 mm of Ostium	32.4% (78/241)
Renal Arteries Treated	
Unilateral	67.6% (163/241)
Bilateral	32.4% (78/241)
Suboptimal PTA Outcome	
Residual Stenosis ≥ 50%	90.7% (214/236)
10 mmHg mean gradient or 20 mmHg peak systolic gradient	25.0% (59/236)
Flow-limiting dissection (NHLBI grade D) or TIMI flow < 3	4.7% (11/236)
Target Lesion Stenosis	81.3 ± 10.0 (241)

Table 13: Baseline Angiographic Data (core lab reported)

Measure	Mean ± SD (range, total lesions)
Lesion Length (mm)	8.5 ± 3.1 (1.8 - 22.1, n = 241)
Pre-procedure	
RVD (mm)	5.34 ± 1.1 (2.9 - 7.9, n = 241)
MLD (mm)	1.8 ± 0.7 (0.3 – 3.8, n = 241)
Percent Diameter Stenosis (%)	65.9 ± 11.4 (37.8 – 92.9, n = 241)

D. Safety and Effectiveness Results

i. Safety Results

The safety endpoint for the HERCULES study is the composite rate of freedom from major adverse events (MAEs), including all cause death, ipsilateral nephrectomy, and embolic events resulting in kidney damage, all through 30 days, and clinically indicated target lesion revascularization (TLR) up to 270 days. Through the first 30 days, there was 1 death and 2 embolic events resulting in kidney damage. The freedom from MAEs and clinically indicated TLRs at 9 months was 94.8%, as shown in Table 14 and the Kaplan-Meier analysis (Figure 1).

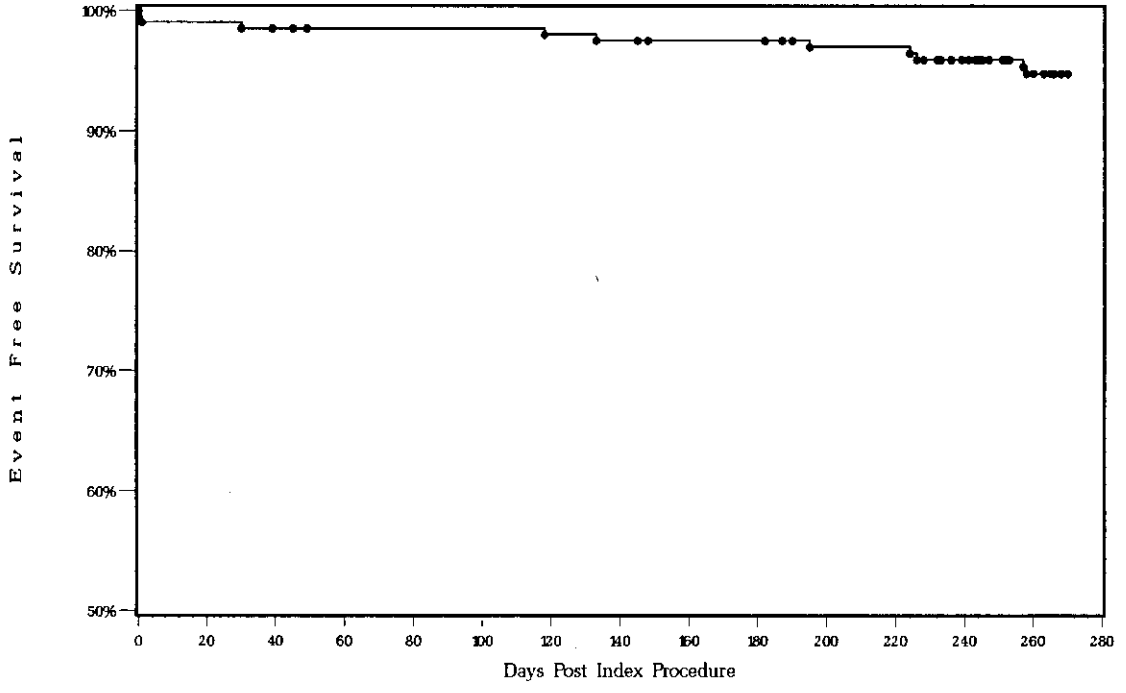
Adverse effects that occurred in the PMA clinical study

Table 14: Protocol Defined Major Adverse Events through 9 Months

MAEs Through 30-Days	**(N=202 Subjects) (N= 241 Lesions)**	**[95% CI][1]**
All-cause death	0.5%	[0.0%, 2.7%]
Device-related death	0.0%	[0.0%, 1.8%]
Embolic events resulting in kidney damage	1.0%	[0.1%, 3.5%]
Nephrectomy	0.0%	[0.0%, 1.8%]
Clinically indicated TLR	0.0%	[0.0%, 1.8%]
Stent thrombosis	0.0%	[0.0%, 1.8%]
Retroperitoneal bleed	0.5%	[0.0%, 2.7%]
Myocardial Infarction	0.0%	[0.0%, 1.8%]
Stroke	0.0%	[0.0%, 1.8%]
Events Through 9 Months (312 Days)	**(N=202 Subjects) (N= 241 Lesions**	**[95% CI][1]**
Renal Failure	1.0%	[0.1%, 3.5%]
Renal Insufficiency	2.0%	[0.5%, 5.0%]
Events Through 9 Months (312 Days)[2]	**(N=202 Subjects) (N= 241 Lesions**	**[95% CI]**
All TLR	7.4%	[3.9%, 10.9%]
Clinically Indicated TLR	5.9%	[2.6%, 9.2%]
Death	2.6%	[0.3%, 5.0%]

[1]By Clopper Pearson exact confidence interval
[2]Based on Kaplan Meier estimate

Figure 1: Freedom from Death, Ipsilateral Nephrectomy and Embolic Events Resulting in Kidney Damage through 30 Days and Clinically Indicated Target Lesion Revascularization through 270 Days (Intent-to-Treat Population)



Days Post Index Procedure	0	(0, 30]	(30, 180]	(180, 270]
Subjects at Risk	202	201	198	191
Subjects Censored	0	1	5	186
Number of Events	1	2	2	5
Event Free (%)	99.5%	98.5%	97.5%	94.8%
Standard Error (%)	0.5%	0.9%	1.1%	1.6%

ii. Effectiveness Results

Two hundred forty-two (242) RX Herculink stents were placed to treat 241 renal artery lesions. By core lab assessment, the mean post-procedure percent diameter stenosis was 3.4% (Table 15). Therefore, the RX Herculink Elite Renal Stent System was effective in establishing patency at the conclusion of the procedure.

Table 15: Post-Procedure Angiographic Data (core lab reported)

Measure	Mean ± SD (range, total lesions)
Post-procedure	
MLD (mm)	5.1 ± 0.8 (3.4 - 7.3, n=240)
Percent Diameter Stenosis (%)	3.4 ± 12.5 (-43.1 - 29.8, n=240)

Primary Endpoint

The 9-month binary restenosis rate met the performance goal. The 9-month binary restenosis rate was 10.5% and the upper limit of the 95% one-sided confidence interval was 14.7%, which is below the pre-specified performance goal of 28.6% ($p < 0.0001$). These results demonstrate the effectiveness of the RX Herculink Elite Renal Stent System in treating atherosclerotic lesions of the renal arteries following suboptimal angioplasty.

Table 16: Primary Endpoint Analysis – Binary Restenosis Rate (ITT Population)

Measure	Mean ± SD (range, total lesions)
9-Month In-Stent Binary Restenosis (≥ 60%) Rate	10.5% (22/209)
[One-Sided 95% Conf. Interval][1]	[-, 14.7%]
One-Sided Exact Binomial Test *p*-value[2]	< 0.0001

[1] By Clopper-Pearson exact confidence interval
[2] One-sided p-value is computed using the exact binomial test with the objective performance criterion (OPC) of 28.6%

Secondary Endpoints

Secondary endpoint analyses included MAEs, device-related success measures (i.e., technical success, acute procedural success, and 30-day clinical success), blood pressure-related outcomes (i.e., systolic and diastolic blood pressure, use of anti-hypertensive medications), renal function (as measured by serum creatinine), and primary and secondary patency.

Device-related success measures ranged from 96.0% to 99.2%. Device success (successful delivery and deployment of a RX Herculink Elite stent), acute procedural success (< 30% residual stenosis post-procedure by core lab analysis), and acute clinical success (procedure success without MAE or access site event requiring surgical or percutaneous intervention prior to hospital discharge) outcomes are summarized in Table 17. These results support the safety and effectiveness of the RX Herculink Elite Renal Stent System in establishing renal artery patency.

Table 17: Device-related Acute Success Measures

Effectiveness	(N = 202 Subjects) (M = 241 Lesions)	[95% CI][1]
Study Device Success	96.0% (237/247)	[92.7%, 98.0%]
Procedural Success	99.2% (238/240)	[97.0%, 99.9%]
Clinical Success	98.0% (197/201)	[95.0%, 99.5%]

[1]By Clopper-Pearson exact confidence interval

Blood pressure-related outcomes demonstrated decreased systolic blood pressure from pre-procedure to 9-month follow-up. The baseline mean systolic and diastolic blood pressures were 162.3 ± 18.5 mmHg and 77.7 ± 11.5 mmHg, respectively. At 9 months mean systolic and diastolic blood pressures were 145.3 ± 21.3 mmHg and 75.4 ± 11.5 mmHg, respectively. When compared to baseline, the mean SBP was reduced at all time points (Table 18). The blood pressure data indicate that over 40% of subjects achieved the SBP <140 mmHg at 9 months after renal stenting. The proportion of patients with SBP < 160 mmHg was increased to 76.3% at 9 months from the 56.4% at baseline. The proportion of patients with SBP ≥ 180 was decreased to 5.2% at 9 months from 19.3% at baseline (Table 19). These data demonstrate the clinical utility of the RX Herculink Elite Renal Stent System and suggest that revascularization with the RX Herculink Elite Renal Stent System does not adversely affect blood pressure outcomes.

Table 18: Blood Pressure Results

Blood Pressure	Mean ± SD (95% CI[1])	
	Systolic (mmHg)	Diastolic (mmHg)
Pre-procedure	162.3 ± 18.5 (202) [159.8, 164.9]	77.7 ± 11.5 (202) [76.1, 79.3]
Post-Procedure	141.3 ± 20.8 (197) [138.3, 144.2]	67.8 ± 11.4 (197) [66.2, 69.4]
1 Month	144.9 ± 20.6 (183) [141.9, 147.9]	75.5 ± 11.2 (183) [73.9, 77.2]
6 Months	146.7 ± 23.1 (158) [143.1, 150.4]	74.8 ± 11.2 (158) [73.1, 76.6]
9 Months	145.3 ± 21.3 (173) [142.1, 148.5]	75.4 ± 11.5 (173) [73.6, 77.1]

[1] By normal approximation

Table 19: Systolic Blood Pressure Goal Analyses

Time Period	Subjects (%) (N)	95% CI[1]
Pre-Procedure		
< 140 (mmHg)	0.5% (1/202)	[0.0%, 2.7%]
≥ 140 and < 160 (mmHg)	55.9% (113/202)	[48.8%, 62.9%]
≥ 160 and < 180 (mmHg)	24.3% (49/202)	[18.5%, 30.8%]
≥ 180 (mmHg)	19.3% (39/202)	[14.1%, 25.4%]
Post-Procedure		
< 140 (mmHg)	46.2% (91/197)	[39.1%, 53.4%]
≥ 140 and < 160 (mmHg)	37.1% (73/197)	[30.3%, 44.2%]
≥ 160 and < 180 (mmHg)	12.2% (24/197)	[8.0%, 17.6%]
≥ 180 (mmHg)	4.6% (9/197)	[2.1%, 8.5%]
30-Day		
< 140 (mmHg)	42.1% (77/183)	[34.8%, 49.6%]
≥ 140 and < 160 (mmHg)	33.9% (62/183)	[27.1%, 41.2%]
≥ 160 and < 180 (mmHg)	17.5%, (32/183)	[12.3%, 23.8%]
≥ 180 (mmHg)	6.6% (12/183)	[3.4%, 11.2%]
6-Month		
< 140 (mmHg)	41.8% (66/158)	[34.0%, 49.9%]
≥ 140 and < 160 (mmHg)	33.5% (53/158)	[26.2%, 41.5%]
≥ 160 and < 180 (mmHg)	15.2% (24/158)	[10.0%, 21.8%]
≥ 180 (mmHg)	9.5% (15/158)	[5.4%, 15.2%]
9-Month		
< 140 (mmHg)	40.5% (70/173)	[33.1%, 48.2%]
≥ 140 and < 160 (mmHg)	35.8% (62/173)	[28.7%, 43.5%]
≥ 160 and < 180 (mmHg)	18.5% (32/173)	13.0%, 25.1%
≥ 180 (mmHg)	5.2% (9/173)	[2.4%, 9.6%]

[1] By Clopper-Pearson exact confidence interval

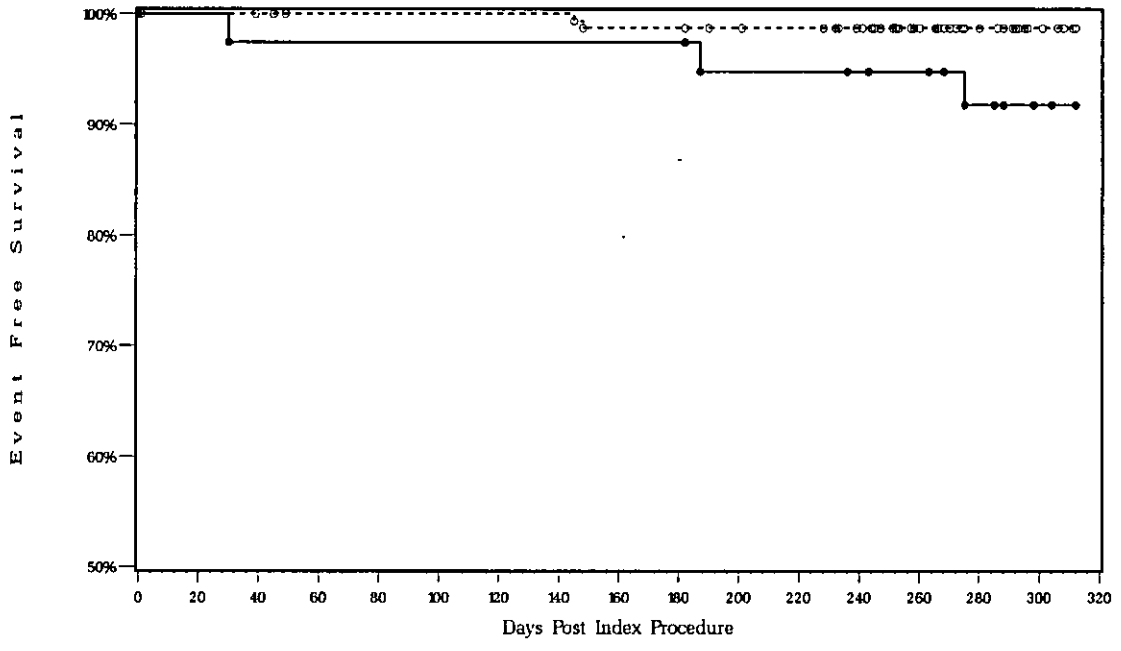
Primary and secondary patency were also assessed at 9 months. The primary patency rate was 88.0% (184/209) and the secondary patency rate was 95.2% (198/208). In addition, renal function was maintained (i.e., did not worsen) from pre-procedure to 9-month follow-up based on serum creatinine levels and eGFR, indicating that revascularization with the Herculink Elite stent does not adversely affect renal function.

iii. Subgroup Analyses

Unilateral vs. Bilateral Lesions

A subgroup analysis has been performed on subjects who were treated for unilateral versus bilateral lesions. Analyses at follow-up visits showed similar results between the unilateral and bilateral treatment groups. However, the Kaplan-Meier analysis showed a significant increase of mortality over the 9 months period in the bilateral group: 5.2% in bilateral vs. 1.3% in unilateral group (log rank p value = 0.0214) (Figure 2).

Figure 2: Subgroup Analysis - Freedom from Death through 312 Days (Intent-to-Treat Population: Bilateral vs. Unilateral)



Solid line: Bilateral Lesion Subjects (n= 39)
Dashed line: Unilateral Lesion Subjects (n= 163)

Days Post Index Procedure	0	(0, 30]	(30, 180]	(180, 270]	(270, 312]
Bilateral					
Subjects at Risk	39	39	38	38	32
Subjects Censored	0	0	0	5	31
Number of Events	0	1	0	1	1
Event Free (%)	100%	97.4%	97.4%	94.8%	91.8%
Standard Error (%)	0.0%	2.5%	2.5%	3.6%	4.5%
Unilateral					
Subjects at Risk	163	163	162	157	135
Subjects Censored	0	1	3	22	135
Number of Events	0	0	2	0	0
Event Free (%)	100%	100%	98.7%	98.7%	98.7%
Standard Error (%)	0.0%	0.0%	0.9%	0.9%	0.9%
Tests Between Groups	Test	Chi-Square	DF	p-value	
	Log-Rank	5.293	1	0.0214	
	Wilcoxon	4.932	1	0.0264	

Gender

The proportions of male and female patients in the HERCULES study are consistent with those in other single-arm studies of renal stents and the available data in the clinical literature on the gender-specific prevalence of renovascular hypertension in the general population. No gender differences are known regarding the treatment of renal hypertension and renal artery stenosis. Patient demographics were similar for male and female patients, though there were differences in tobacco use and coronary artery disease between the two groups (Table 20).

Table 20: Patient Demographics by Gender

	Male N = 76	Female N = 126	Difference [95% CI][1]
Age (in years)			
Mean ± SD (n)	69.5 ± 9.4 (76)	73.7 ± 9.1 (126)	-4.3
Range (min, max)	(47.7, 88.6)	(44.0, 88.2)	
[95% Confidence Interval][1]	[67.3, 71.6]	[72.1, 75.3]	[-6.9, -1.6]
Race			
American Indian or Alaska Native	0.0% (0/76)	0.0% (0/126)	0.0% [3]
Asian	1.3% (1/76)	0.0% (0/126)	1.3% [3]
African American	1.3% (1/76)	11.9% (15/126)	-10.6% [3]
Latino-Hispanic	7.9% (6/76)	7.1% (9/126)	0.8% [-6.8%, 8.3%]
Native Hawaiian or Other Pacific Islander	1.3% (1/76)	0.0% (0/126)	1.3% [3]
Caucasian	88.2% (67/76)	81.0% (102/126)	7.2% [-2.8%, 17.2%]
Decline to answer	0.0% (0/76)	1.6% (2/126)	-1.6% [3]
Risk Factor Profile			
Diabetes	50.0% (38/76)	42.1% (53/126)	7.9% [-6.2%, 22.1%]
[95% Confidence Interval][2]	[38.3%, 61.7%]	[33.3%, 51.2%]	
Type 1	3.9% (3/76)	3.2% (4/126)	0.8% [3]
Type 2	46.1% (35/76)	38.9% (49/126)	7.2% [-6.9%, 21.2%]
Tobacco Use	71.1% (54/76)	48.4% (61/126)	22.6% [9.2%, 36.1%]
[95% Confidence Interval][2]	[59.5%, 80.9%]	[39.4%, 57.5%]	
Former	57.9% (44/76)	35.7% (45/126)	22.2% [8.3%, 36.1%]
Current	13.2% (10/76)	12.7% (16/126)	0.5% [-9.1%, 10.0%]
Hypercholesterolemia	92.1% (70/76)	82.5% (104/126)	9.6% [0.6%, 18.5%]
[95% Confidence Interval][2]	[83.6%, 97.0%]	[74.8%, 88.7%]	
Requiring Medication	86.8% (66/76)	79.4% (100/126)	7.5% [-2.9%, 17.9%]
Not Requiring Medication	5.3% (4/76)	3.2% (4/126)	2.1% [3]
Coronary Artery Disease	77.6% (59/76)	61.1% (77/126)	16.5% [3.9%, 29.2%]
[95% Confidence Interval][2]	[66.6%, 86.4%]	[52.0%, 69.7%]	

[1] By normal approximation
[2] By Clopper-Pearson exact confidence interval
[3] Assumptions not met

Tables 21 to 25 contain a summary of the key primary and secondary endpoints, stratified by gender. None of these analyses were pre-specified. There were no differences in the

rates of MAEs through 9 months for males or females (Table 21). There were also no differences in the rates of binary restenosis for males or females (Table 22).

Table 21: Protocol Defined Major Adverse Events through 9 Months

MAEs Through 30-Days	Male (N=76 Subjects) (N= 90 Lesions)	Female (N=126 Subjects) (N= 151 Lesions)
All-cause death	1.3% (1/76) [0.0%, 7.1%]	0.0% (0/126) [0.0%, 2.9%]
Device-related death	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Embolic events resulting in kidney damage	1.3% (1/76) [0.0%, 7.1%]	0.8% (1/126) [0.0%, 4.3%]
Nephrectomy	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Clinically indicated TLR	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Stent thrombosis	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Retroperitoneal bleed	0.0% (0/76) [0.0%, 4.7%]	0.8% (1/126) [0.0%, 4.3%]
Myocardial Infarction	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Stroke	0.0% (0/76) [0.0%, 4.7%]	0.0% (0/126) [0.0%, 2.9%]
Events Through 9 Months (312 Days)		
Renal Failure	0.0% (0/76) [0.0%, 4.7%]	1.6% (2/126) [0.2%, 5.6%]
Renal Insufficiency	2.6% (2/76) [0.3%, 9.2%]	1.6% (2/126) [0.2%, 5.6%]
Events Through 9 Months (312 Days)[2]		
All TLR	2.5% [0.0%, 5.8%]	10.5% [5.0%, 16.0%]
Clinically Indicated TLR	2.5% [0.0%, 5.8%]	8.0% [3.1%, 12.9%]
Death	4.0% [0.0%, 8.5%]	1.8% [0.0%, 4.3%]

[1]By Clopper Pearson exact confidence interval
[2]Based on Kaplan Meier estimate

Table 22: In-Stent Binary Restenosis by Gender

Gender	Male N = 76 M = 90 lesions	Female N = 126 M = 151 lesions	Difference [95% CI][1]
9-Month In-Stent Binary Restenosis [95% Confidence Interval][2]	11.7% (9/77) [5.5%, 21.0%]	9.8% (13/132) [5.3%, 16.3%]	1.8% [-7.0%, 10.6%]

[1] By normal approximation
[2] By Clopper-Pearson exact confidence interval

Table 23 presents the acute device, procedural and clinical success rates, stratified by gender. The rates were comparable for male and female patients. Table 24 contains a summary of systolic and diastolic blood pressure measurements pre-procedure and at the 9 months follow-up by gender. At 9 months, the mean SBP was reduced for both male and female subjects, with no difference between male and female subjects. Table 25 includes a summary of eGFR by gender. There were no differences in eGFR between male and female patients.

Table 23: Acute Success by Gender

Gender	Male	Female
Study Device Success	95.7% (89/93) [89.4%, 98.8%]	96.1% (148/154) [91.7%, 98.6%]
Procedure Success	100.0% (89/89) [95.9%, 100.0%]	98.7% (149/151) [95.3%, 99.8%]
Clinical Success	98.7% (74/75) [92.8%, 100.0%]	97.6% (123/126) [93.2%, 99.5%]

Table 24: Summary of Blood Pressure Measurements – Per Subject Analysis - (Intent-to Treat Population: Male vs. Female

	Male N = 76	Female N = 126	Difference [95% CI][1]
Pre-Procedure			
Systolic (mmHg)			
Mean ± SD (n)	157.1 ± 15.5 (76)	165.5 ± 19.4 (126)	-8.4
Median (Q1, Q3)	153.0 (145.5, 162.8)	160.0 (150.0, 179.0)	
Range (min, max)	(134.0, 208.0)	(140.0, 222.0)	
[95% Confidence Interval][1]	[153.5, 160.6]	[162.1, 168.9]	[-13.3, -3.5]

Table 24: Summary of Blood Pressure Measurements – Per Subject Analysis - (Intent-to Treat Population: Male vs. Female

	Male N = 76	Female N = 126	Difference [95% CI][1]
Diastolic (mmHg)			
Mean ± SD (n)	77.7 ± 10.7 (76)	77.6 ± 12.0 (126)	0.1
Median (Q1, Q3)	77.0 (70.0, 84.5)	77.5 (70.0, 85.5)	
Range (min, max)	(51.5, 102.0)	(49.5, 118.5)	
[95% Confidence Interval][1]	[75.3, 80.2]	[75.5, 79.8]	[-3.1, 3.3]
At 9 months [228, 312 days]			
Systolic (mmHg)			
Mean ± SD (n)	143.4 ± 17.7 (62)	146.4 ± 23.2 (111)	-3.0
Median (Q1, Q3)	139.5 (130.0, 157.0)	143.0 (133.0, 160.0)	
Range (min, max)	(112.0, 190.0)	(90.0, 242.5)	
[95% Confidence Interval][1]	[138.9, 147.9]	[142.1, 150.8]	[-9.2, 3.2]
Diastolic (mmHg)			
Mean ± SD (n)	76.9 ± 11.0 (62)	74.5 ± 11.7 (111)	2.4
Median (Q1, Q3)	75.0 (69.0, 83.0)	73.5 (66.0, 83.0)	
Range (min, max)	(57.0, 102.0)	(49.0, 122.0)	
[95% Confidence Interval][1]	[74.1, 79.7]	[72.3, 76.7]	[-1.1, 5.9]

[1] By normal approximation

Table 25: Summary of Estimated Glomerular Filtration Rate (eGFR) – Per Subject Analysis - (Intent-to-Treat Population: Male vs. Female)

Estimated Glomerular Filtration Rate (eGFR; in mL/min/1.73m^2)	Male N = 76	Female N = 126	Difference [95% CI][1]
Pre-Procedure			
Mean ± SD (n)	60.9 ± 21.8 (76)	56.2 ± 20.1 (124)	4.8
Median (Q1, Q3)	57.8 (44.0, 71.9)	52.8 (41.7, 66.9)	
Range (min, max)	(28.4, 123.4)	(22.1, 128.3)	
[95% Confidence Interval][1]	[56.0, 65.9]	[52.6, 59.7]	[-1.3, 10.9]
At 9 months [228, 312 days]			
Mean ± SD (n)	60.7 ± 23.3 (59)	55.0 ± 22.0 (106)	5.7
Median (Q1, Q3)	61.0 (44.3, 71.4)	51.6 (38.4, 66.4)	
Range (min, max)	(11.3, 126.9)	(11.2, 133.2)	
[95% Confidence Interval][1]	[54.6, 66.8]	[50.8, 59.2]	[-1.6, 13.0]

[1] By normal approximation

Note: eGFR = 186 x $(S_{cr})^{-1.154}$ x $(age)^{-0.203}$ x 0.742 (if female) x 1.210 (if African-American)

The analyses presented in Tables 20 - 25 suggest that it is valid to pool data for males and females, and that the overall results of this study can be generalized to both genders.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

There is no supplemental clinical information associated with this PMA.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTIONS

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the RX Herculink Elite Renal Stent System are based on data collected in a clinical study conducted to support PMA approval as described above. The freedom from major adverse event rate, defined as death for any reason at 30 days, ipsilateral nephrectomy at 30 days, clinically-driven target lesion revascularization up to 9 months, and embolic events resulting in kidney damage at 30 days, was 94.8%. The composite rate of death, ipsilateral nephrectomy and embolic events resulting in renal damage at 30 days was 1.5%.

Comprehensive preclinical bench testing was performed on the RX Herculink Elite Renal Stent System (both the stent and the delivery system) in accordance with national and international standards and guidance documents. The testing demonstrated that the RX Herculink Elite Renal Stent System met its performance and design specifications.

Preclinical *in vivo* animal testing was conducted on 17 animals in order to evaluate the acute and chronic performance of the RX Herculink Elite Renal Stent System. The studies were performed to evaluate deployment and histopathological response in swine models for 3, 28 and 181 days. The results support the safety and expected performance of the RX Herculink Elite Renal Stent System.

Biocompatibility testing was performed on the RX Herculink Elite Renal Stent System in accordance with applicable standards. All testing met the requirements as specified in the applicable standard, ensuring the finished device is biocompatible.

Sterilization, packaging, and shelf life testing were performed on the RX Herculink Elite Renal Stent System. The testing demonstrated that the RX Herculink Elite Renal Stent System maintains a Sterility Assurance Level of 10^{-6}. The results of shelf life testing confirmed that the RX Herculink Elite Renal Stent System maintains functionality throughout its16-month shelf life, and the packaging testing demonstrated that the packaging adequately protects the device throughout its 16-month shelf life.

B. Effectiveness Conclusions

Results of the HERCULES study demonstrate the safety and effectiveness of the RX Herculink Elite Renal Stent in the treatment of *de novo* or restenotic atherosclerotic lesions (≤ 15 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 - 7.0 mm following suboptimal PTRA, defined as ≥ 50% residual stenosis, ≥ 20 mmHg peak systolic or ≥ 10 mmHg mean translesional pressure gradient or flow-limiting dissection.

Specifically, the 9-month binary restenosis rate (10.5%), with the upper one-sided 95% CI of 14.7%, exceeded the performance goal of 28.6% ($p < 0.0001$), and use of the RX Herculink Elite Renal Stent System was associated with a low MAE rate, improvement in blood pressure, maintenance of renal function and acute device success, acute procedure success, and acute clinical success rates of 96.0%, 99.2% and 98.0%, respectively.

C. Overall Conclusions

The results of the HERCULES study provide a reasonable assurance of the safety and effectiveness of the RX Herculink Elite Renal Stent System in the treatment of *de novo* or restenotic atherosclerotic lesions (≤ 15 mm in length) located within 10 mm of the renal ostium and with a reference vessel diameter of 4.0 - 7.0 mm following suboptimal angioplasty. The data presented formed the basis for FDA's finding that the RX Herculink Elite Renal Stent System is safe and effective for its intended use.

XIV. CDRH DECISION

FDA issued an approval order on July 20, 2011. As a condition of PMA approval, the sponsor is required to follow the existing 202-patient HERCULES study cohort for a total of three years to assess the long-term safety and effectiveness of the device.

XV. APPROVAL SPECIFICATIONS

Instructions for Use: See labeling.

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

Postapproval Requirements and Restrictions: See approval order.

XVI. REFERENCES

None