SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Renal Stent with Delivery System
Device Trade Names:	Formula™ Balloon-Expandable Renal Stent System (Formula™ 418 Renal Stent System; Formula™ 414 RX Renal Stent System)
Applicant's Name and Address:	Cook Incorporated 750 Daniels Way PO Box 489 Bloomington, IN 47404
Date of Panel Recommendation:	Not applicable
Premarket Approval (PMA) Application Number:	P100028
Date of Notice of Approval to Applicant:	January 14, 2010
Expedited:	Not Applicable

II. INDICATIONS FOR USE

The Formula™ Balloon-Expandable 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 lesion (≤ 18 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 systolic or ≥ 10 mmHg mean translesional pressure gradient, or flow-limiting dissection.

III. CONTRAINDICATIONS

The Formula™ Balloon-Expandable Renal Stent System is contraindicated for use in:

- Patients for whom antiplatelet and/or anticoagulant therapy is contraindicated.
- Patients who have a lesion that cannot be crossed with a wire or a balloon angioplasty catheter.
- Patients who have stenoses that cannot be dilated to permit passage of the stent.
- Patients with bleeding disorders.

- 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. WARNING AND PRECAUTIONS

The warnings and precautions can be found in the Formula™ Balloon-Expandable Renal Stent labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The Formula™ Balloon-Expandable Renal Stent (also referred to as the Formula™ stent) is comprised of a 316L stainless steel stent pre-mounted on a delivery system. The stent is composed of repeating cells, each of which consists of a "main" segment and a "flex" segment that acts to connect the cells. The ends of the stent are terminated with the "main" segments. The stent is intended 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 lesion (≤ 18 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 systolic or ≥10 mmHg mean translesional pressure gradient, or flow-limiting dissection. 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 Formula™ Stents

Diameter	Length		
	12 mm	16 mm	20 mm
4 mm	X	X	X
5 mm	X	X	X
6 mm	X	X	X
7 mm	X	X	X

The delivery system is available in two versions, an "over-the-wire" version and a "rapid-exchange" version. The choice of delivery system is at the discretion of the clinician. The stent with the over-the-wire delivery system is designated Formula™ 418 Renal Stent System, while the stent with the rapid-exchange delivery system is designated Formula™ 414 RX Renal Stent System. The delivery system of the Formula™ 418 Renal Stent System consists of a double-lumen co-axial catheter: one lumen is used to pass a wire guide, and the other lumen is used to expand the balloon. The delivery system of the Formula™ 414 RX Renal Stent System has a single lumen for most of its length, with the

distal 25 cm having two lumens. The main lumen is for balloon expansion; the second lumen is for passage of the wire guide. Common features of both versions are: 1) a semi-compliant balloon for expansion of the stent, 2) radiopaque markers under the proximal and distal ends of the stent to promote accurate placement under fluoroscopy, and 3) catheter lengths of 80 cm or 135 cm. The balloon has a rated burst pressure of 12 atm.

The crossing profile for the Formula™ 418 delivery system is ≤ 0.066" for the 4–6 mm stents and ≤ 0.079" for the 7 mm stent. The crossing profile for the Formula™ 414 delivery system is ≤ 0.068". The delivery systems of both versions are compatible with a 5 Fr sheath and a 6 Fr guiding catheter regardless of stent diameter, except the delivery system of the 7 mm Formula™ 418 stent, which is compatible with a 6 Fr sheath and 7 Fr guiding catheter.

The Formula™ Balloon-Expandable Renal Stent is pre-mounted on the delivery system. In use, the stent is delivered to the diseased renal artery via percutaneous arterial access under fluoroscopic control, using standard techniques for placement of arterial access sheaths, guiding catheters/introducers, and wire guides. To deploy the stent, the balloon is inflated to its recommended expansion pressure, expanding the stent to a diameter equal to or slightly larger than that of the reference vessel. The balloon is then deflated and withdrawn leaving the stent in place. The device is intended for use by physicians trained and experienced in diagnostic and interventional techniques, in general, and renal stenting techniques and procedures, in particular.

Table 2: Formula™ Balloon-Expandable Renal Stent System Model Numbers

Formula™ 418				Formula™ 414 RX			
Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)	Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)
FOR418-18-80-4-12	80	4	12				
FOR418-18-80-4-16	80	4	16				
FOR418-18-80-4-20	80	4	20				
FOR418-18-80-5-12	80	5	12	FORX414-14-80-5-12	80	5	12
FOR418-18-80-5-16	80	5	16	FORX414-14-80-5-16	80	5	16
FOR418-18-80-5-20	80	5	20	FORX414-14-80-5-20	80	5	20
FOR418-18-80-6-12	80	6	12	FORX414-14-80-6-12	80	6	12
FOR418-18-80-6-16	80	6	16	FORX414-14-80-6-16	80	6	16
FOR418-18-80-6-20	80	6	20	FORX414-14-80-6-20	80	6	20
FOR418-18-80-7-12	80	7	12	FORX414-14-80-7-12	80	7	12
FOR418-18-80-7-16	80	7	16	FORX414-14-80-7-16	80	7	16
FOR418-18-80-7-20	80	7	20	FORX414-14-80-7-20	80	7	20
FOR418-18-135-4-12	135	4	12				
FOR418-18-135-4-16	135	4	16				
FOR418-18-135-4-20	135	4	20				

Table 2: Formula™ Balloon-Expandable Renal Stent System Model Numbers

Formula™ 418				Formula™ 414 RX			
Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)	Model	Catheter Length (cm)	Stent Diameter (mm)	Stent Length (mm)
FOR418-18-135-5-12	135	5	12	FORX414-14-135-5-12	135	5	12
FOR418-18-135-5-16	135	5	16	FORX414-14-135-5-16	135	5	16
FOR418-18-135-5-20	135	5	20	FORX414-14-135-5-20	135	5	20
FOR418-18-135-6-12	135	6	12	FORX414-14-135-6-12	135	6	12
FOR418-18-135-6-16	135	6	16	FORX414-14-135-6-16	135	6	16
FOR418-18-135-6-20	135	6	20	FORX414-14-135-6-20	135	6	20
FOR418-18-135-7-12	135	7	12	FORX414-14-135-7-12	135	7	12
FOR418-18-135-7-16	135	7	16	FORX414-14-135-7-16	135	7	16
FOR418-18-135-7-20	135	7	20	FORX414-14-135-7-20	135	7	20

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 Formula™ Balloon-Expandable Stent has been commercially available in the US for treatment of biliary strictures since February 2006 (on the 418 delivery system). The Formula™ Balloon-Expandable Stent has been commercially available for treatment of renal artery stenosis outside the US, including Asia, Europe, Middle East/Africa, and South America, since May 2006 (on the 414 delivery system) and February 2009 (on the 418 delivery system).

No products have been withdrawn from the market 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 stainless steel 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. BIOCOMPATIBILITY

A thorough panel of biocompatibility testing was performed on the Formula™ stent and both delivery systems in accordance with FDA's biocompatibility testing guidance, Use of International Standard ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (May 1, 1995) 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 Formula™ Balloon Expandable Renal Stent System for clinical use.

Table 3: Biocompatibility Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Biocompatibility Test	Test Article	Purpose	Acceptance Criteria	Result
ISO Elution Method	Stent and delivery systems	To determine the potential for cytotoxicity.	Not more than 50% lysis	Pass
ISO Maximization Sensitization Study	Stent and delivery systems	To evaluate the potential for delayed dermal contact sensitization.	No evidence of sensitization, based on observation of erythema and edema	Pass
ISO Intracutaneous Study	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.	Primary Irritation Index < 1.9	Pass
USP and ISO Systemic Toxicity Study	Stent and delivery systems	To determine the potential for systemic toxicity.	No evidence of significant systemic toxicity, defined as death of 2 or more animals, abnormal behavior in 2 or more animals, or 2 grams or more weight loss in 3 or more animals	Pass
In Vitro Chromosomal Aberration Study in Mammalian Cells	Stent	To determine whether the abstract would cause genotoxicity in Chinese Hamster Ovary (CHO) cells in the presence and absence of S9 metabolic activation.	No evidence of significant genotoxicity in Chinese Hamster ovary cells (0.05 significance; $\chi^2 > 3.841$)	Pass

Table 3: Biocompatibility Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Biocompatibility Test	Test Article	Purpose	Acceptance Criteria	Result
Bacterial Reverse Mutation Study (Dimethyl Sulfoxide (DMSO) Extract)	Stent	To evaluate whether a DMSO extract of the abstract would cause mutagenic changes in the presence and absence of S9 metabolic activation.	Less than 2-fold increase in the number of mean revertants of any tested strains	Pass
Bacterial Reverse Mutation Study (Saline Extract)	Stent	To evaluate whether a saline extract of the abstract would cause mutagenic changes in the presence and absence of S9 metabolic activation.	Less than 2-fold increase in the number of mean revertants of any tested strains	Pass
ISO Muscle Implantation Study in Rabbits, 4 Week	Stent	To evaluate the evidence of irritation or toxicity at 4 weeks.	No significant macroscopic reaction and non-irritating upon microscopic examination of implantation	Pass
ISO Muscle Implantation Study in Rabbits, 12 Week	Stent	To evaluate the evidence of irritation or toxicity at 12 weeks.	No significant macroscopic reaction and non-irritating upon microscopic examination of implantation	Pass
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
Plasma Recalcification Time Coagulation Study	Stent and delivery systems	To determine the potential of the test article to cause an effect on the coagulation cascade.	No effect on recalcification time	Pass
Implantation in Porcine Renal Arteries Study	Stent	To determine whether the test article causes significant thrombogenicity.	No evidence of significant thrombogenicity	Pass

Tests for carcinogenicity, in vivo thrombogenicity, and chronic toxicity testing were not performed due to the extensive clinical history of the device materials and their well-characterized long-term safety profile. Implantation testing was performed in a porcine model as part of the animal studies conducted for the device.

The test results demonstrate that both the stent and delivery system are biocompatible and non-pyrogenic.

B. Animal Studies

Two animal studies were conducted to evaluate device safety and overall product performance. One study was conducted to assess the 30-day biological response of renal arteries to the stent under conditions that simulate the intended use of the device. A second study was conducted to assess delivery system performance and stent deployment. Both

animal studies were conducted in accordance with Good Laboratory Practices (GLP) requirements. The animal studies performed and the study endpoints are summarized in Table 4.

Table 4: Animal Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Study Objectives	Number of Animals Timepoints Devices Tested	Relevant Findings
One-month Study of Formula™ 418 Balloon-Expandable Renal Stents in Porcine Renal Arteries		
Evaluate vascular response to stents in porcine renal arteries Assess safety of device via , radiographic, physiologic (thrombus), gross and histological tissue observations	• 5 animals • 30 days • 10 Formula 418 stents	• No deaths were reported. • No complications occurred during implantation of the devices. • No changes in animal health were noted following implantation of the devices. • Injury scores were low in the Formula stents at 30 days (mean Schwarz score 0.10 ± 0.13). • Inflammatory scores were low 30 days after stent implantation (mean score 0.17 ± 0.15). • Percent stenosis was low, < 13%. • No aneurysm dilatation.
One-month Study of Formula™ 418 Balloon-Expandable Renal Stents in Porcine Renal Arteries		
Evaluate vascular response to stents in porcine renal arteries Assess safety of device via clinical (complete blood count (CBC) with differentials, serum chemistry), radiographic, physiologic (thrombus), gross and histological tissue observations	• 7 animals • 28 days • 10 Formula 418 stents	• No deaths were reported. • No complications occurred during implantation of the devices. • No changes in animal health were noted following implantation of the devices. • Injury scores were low in the Formula stents at 30 days (mean Schwarz score 0.22 ± 0.18). • Inflammatory scores were low 30 days after stent implantation (mean score 0.20 ± 0.17). • Percent stenosis was low, < 16%. • No aneurysm dilatation.
Evaluate Performance of Formula™ 418 Balloon-Expandable Stent Delivery System in Porcine Arteries		
Evaluate delivery system performance and stent deployment of Formula™ 418 Renal Stent System	• 2 animals • 1 day • 16 Formula 418 stents	All devices considered to have good to excellent delivery, deployment, and withdrawal characteristics.
Evaluate Performance of Formula™ 414 RX Balloon-Expandable Stent Delivery System in Porcine Arteries		

Table 4: Animal Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Study Objectives	Number of Animals Timepoints Devices Tested	Relevant Findings
Evaluate delivery system performance and stent deployment of Formula™ 414 RX Renal Stent System	• 1 animal • 1 day • 12 Formula 414 RX stents	All devices considered to have adequate to excellent delivery, deployment, and withdrawal characteristics.

The animal studies demonstrated that stents did not cause any abnormal localized tissue responses and that 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. Therefore, the animal testing results for the Formula™ Balloon-Expandable Renal Stent support a reasonable assurance of device safety and effectiveness.

C. In-Vitro Bench Testing

Comprehensive *in vitro* laboratory testing was performed on the Formula™ Balloon-Expandable 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* (January 13, 2005). Table 5 summarizes the *in vitro* laboratory testing results. The test results verified that the Formula™ stent and both delivery systems 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 Formula™ Balloon-Expandable Renal Stent System

Type of Study	Objective	Summary of Method and Result
Stent Corrosion Resistance	To characterize the corrosion behavior of the stent	Cyclic potentiodynamic polarization testing was performed to determined breakdown potential of the stent. The test determined that the breakdown potential was higher than (better than) a commercially-marketed stent.
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.

Table 5: In Vitro Laboratory Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Type of Study	Objective	Summary of Method and Result
Foreshortening	To provide assurance that the stent has clinically insignificant foreshortening	The lengths of stents were measured before and after deployment from the balloon catheters. No stent had > 3% foreshortening.
Recoil for Balloon-Expandable Stents	To provide assurance that the stent has clinically insignificant recoil	The diameter of stents were measured while on an inflated balloon and then after release from the balloon. No stent had > 6% recoil.
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	Stents were expanded to maximum stent diameter or until balloon rupture. Examination under magnification detected no clinically significant cracks or flaws.
Radial Stiffness and Radial Strength	To provide assurance that the radial strength of the stent is sufficient to resist permanent deformation under clinically relevant loads and maintain an acceptable diameter under those loads	Stents were compressed to 50% of nominal diameter using an automated radial expansion force gage. Radial force versus diameter was plotted for each stent size. Radial strength and stiffness were determined via characteristics of the plot. The lowest radial stiffness was 2.20 N/mm^2 and the lowest radial force was 1.00 N/mm.
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 annealed stainless steel tubes used to make the stents via standard tensile testing equipment. The average ultimate tensile strength was 89.00-91.14 ksi, depending on the diameter and thickness of the tube.
Finite Element Analysis	To estimate the response of the stent to cyclic radial and bending loading for the purpose of developing parameters for *in vitro* fatigue testing of the stent	Finite element analyses were conducted on the stents, based on three-dimensional models, two-dimensional drawings, and conservative estimates of ultimate tensile strength and endurance limit. Data on mean stress and alternating stress were used to calculate a fatigue safety factor. The safety factor was > 1 for all points in all stents, whereas a similar analysis on similar stents showed lower safety factors.
***In Vitro* Fatigue Testing**	To evaluate the fatigue life of the stent by subjecting it to time-accelerated, physiologically modeled, diameter-controlled pulsatile loading for a clinically-relevant number of cycles	The stent with the lowest safety factor as determined by finite element analysis was subjected to 400 million cycles of radial fatigue testing at 1 mm beyond nominal labeled diameter. No strut fractures were noted in any of the stents after completion of 400 million cycles.

Table 5: In Vitro Laboratory Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Type of Study	Objective	Summary of Method and Result
Bending Fatigue	To determine the bending fatigue endurance limit of the stent (i.e., the smallest radius of curvature at which the stent can withstand the equivalent of 10 years of repeated bending), and compare it to the expected *in vivo* radius of curvature of the stented renal artery due to respiration.	Three initial radii of curvature tested with 4 stents at each radius, with the radii of curvature smaller than the acceptance criteria. Radius of curvature was increased until all test articles did not fracture before 85 million cycles. That radius of curvature was deemed the bending fatigue endurance limit. The 10-year equivalent (85 million cycles) bending endurance limit was found to be 600 mm, meeting the acceptance criterion of 1180 mm.
Magnetic Resonance Imaging (MRI) Safety and Compatibility	To characterize the MRI compatibility of the stent	The stents were subjected to an average whole-body specific absorption ratio of 3 W/kg and a 720 gauss/cm spatial gradient for 15 minutes. There was no observable torque, the deflection was not significantly different than deflection due to gravity, and the stent rose in temperature by no more than 0.1 °C compared to the reference.
Radiopacity	To provide assurance that the radiopacity of the stent is acceptable before and after deployment and radiopacity of the delivery system is acceptable during use	The stent and delivery system were assessed as having good to excellent radiopacity in various *in vivo* renal artery models.
Delivery, Deployment, and Retraction	To provide assurance that stents can be delivered and deployed accurately and easily, and delivery systems withdrawn easily, from renal arteries	Stents and delivery systems were tested in *in vitro* and *in vivo* renal artery models. Stents and delivery systems were introduced, tracked, and withdrawn easily when used with the appropriate size sheaths, wires, and fittings. The proximal ends of the deployed stents were within 2 mm of the proximal end of the target location.
Balloon Rated Burst Pressure	To demonstrate with at least 95% confidence that 99.9% of the balloons shall not burst at or below the rated (labeled) burst pressure (12 atm), with acceptable failure modes when subjected to pressure sufficient to burst the balloon	Balloons at each diameter were inflated until they burst. The lower confidence limit of each diameter was above the rated (labeled) burst pressure. All balloons had acceptable failure modes (linear burst or pinholes).
Balloon Fatigue	To demonstrate with at least 95% confidence that 90% of the balloons can sustain 10 repeated inflations to the rated burst pressure (RBP)	Balloons representing the range of sizes were inflated 10 times. No more than one balloon at each size failed to inflate 10 times.

Table 5: In Vitro Laboratory Testing Summary for the Formula™ Balloon-Expandable Renal Stent System

Type of Study	Objective	Summary of Method and Result
Balloon Compliance	To provide assurance that stents meet their labeled diameter at 8 atm nominal inflation pressure (8 atm) and a reproducible diameter at rated (labeled) burst pressure (12 atm)	Balloons at each diameter were inflated in 1 atm increments and the diameter of the balloon was noted. The average at each diameter was used to develop the stent's compliance chart. All stents were nominal diameter at nominal inflation pressure (8 atm).
Catheter Bond Strength	To provide assurance that the bonds of the catheter (e.g., proximal balloon to shaft) are sufficient to withstand clinically relevant tensile forces (> 3 N to > 10 N, depending on bond)	Individual bonds were pulled on a tensile tester until failure. All bond strengths were greater than the acceptance criteria.
Crossing Profile	To provide assurance that the profile of the stents and delivery systems are compatible with inner diameter of the guide catheters and sheaths specified in the labeling	The profile of delivery systems, including the stent on the delivery systems, were measured to assure that 4 - 6 mm stents were ≤ 0.066" and 7 mm stents were ≤ 0.079".
Balloon Inflation and Deflation Times	To provide assurance that the inflation and deflation times were < 30 seconds when using the specified contrast (up to 50/50 mix of contrast and saline)	Several balloons representing the most difficult balloons to inflate and deflate were tested. The maximum inflation time was 12 seconds; the maximum deflation time was 16 seconds.
Stent Securement for Unsheathed Stents	To provide assurance that the stent would not displace from (move in relation to) or dislodge from (completely separate) the delivery system during passage of the device through the body	Devices were passed through a tortuous *in vitro* model with a simulated stricture. No dislodgement or displacement was observed.

The acceptance criteria were met for each of the above tests.

D. Sterilization, Packaging, and Shelf-Life

The Formula™ Balloon-Expandable Renal Stent System is sterilized by a validated ethylene oxide (EtO) sterilization process to achieve a minimal sterility assurance level (SAL) of 10-6. The EtO and ethylene chlorohydrin levels are in accordance with ISO 10993-7: 2008, *Biological evaluation of medical devices-Ethylene oxide sterilization residual*. Product and package stability testing of the Formula™ Balloon-Expandable Renal Stent was performed and validated for a 1-year and 3-year shelf life for the 414 and 418 delivery systems, respectively.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Results from a multi-center clinical study (IDE G070014, also known as the REFORM ("REnal FORMula Stent") study) demonstrate the safety and effectiveness of the

Formula™ stent. Specifically, the 9-month primary patency rate was 91.7%, meeting the performance goal of 60%. In addition, use of the Formula™ stent 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 REFORM study is presented in Table 6.

Table 6: Overview of the REFORM study

Device	Formula™ Balloon-Expandable Renal Stent System
Study Design	Non-randomized, prospective, single-arm, multi-center clinical study
Patients Enrolled	100 (44 male and 56 female)
Number of Sites	7 investigational sites
Primary Endpoint	Primary patency at 9 months, defined as ≤ 60% diameter stenosis and freedom from intervention since the initial procedure. Analysis done on a per-lesion basis. Patency was assessed by ultrasound analysis (or quantitative angiography, if necessary) by an independent core laboratory.
Secondary Endpoints	MAEs: Incidence of major adverse events, defined as procedure- or device-related events of death, Q-Wave MI, clinically driven target lesion revascularization (TLR), and significant embolic events (defined as unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or kidney failure). MAEs were reported as percentage of patients with MAEs, after 30 days, 9 months, 24 months, and 36 months (from the previous period and cumulative), using all enrolled patients. In addition to MAE rate, the rates of individual events (death, Q-Wave MI, clinically driven target lesion revascularization (TLR), unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, and kidney failure) will also be reported (from the previous period and cumulative), using all enrolled patients. Change in blood pressure: Systolic and diastolic blood pressures were measured at baseline and 1, 9, 24, and 36 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. Change in Antihypertensive Medications: Number and dosage of antihypertensive medications at baseline and at 1, 6, 9, 12, 18, 24, and 36 months was collected. The group average number of antihypertensive medications at each time point was reported. In addition, data was reported as a percentage of patients at 9 months with a decrease in medication (in dose or amount), no change in medication, or increase in medication compared to baseline. Change in Renal Function: Improvement and/or stabilization of renal function (as measured by estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation) were measured at baseline and at 1, 9, 24, and 36 months, with the group average reported at each time point. The change at 9 months from baseline was calculated for each enrolled patient. Technical Success: Technical success is defined as successful delivery and

Table 6: Overview of the REFORM study

	deployment of a Formula™ Balloon-Expandable Stent. It was reported as a percentage of enrolled patients. 30-day Clinical Success: 30-day clinical success is defined as a vessel with <30% residual stenosis immediately after stent placement and no major adverse events within 30 days of implant. It was expressed as a percentage of stented arteries and a percentage of enrolled patients. Target Lesion Revascularization: TLR is defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter restenosis of the originally treated site following the initial procedure. It was evaluated at 9 months and reported as a percentage of stented arteries and a percentage of enrolled patients. Acute Procedural Success: Acute procedural success is defined as a vessel with <30% residual stenosis determined angiographically immediately after stent placement and no major adverse events before discharge. It was reported as a percentage of stented arteries and a percentage of enrolled patients.
Study Hypothesis	Renal arteries treated with the Formula™ Balloon-Expandable Stent will have a primary patency rate at 9 months on a per-stented artery basis that meets a performance goal of 60%.
Patient Follow-up	1-month clinic visit: Assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 6-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 9-month clinic visit with ultrasound: Assessments of blood chemistry, blood pressure, antihypertensive medications, adverse events, ultrasound for evidence of stenosis. Patients with non-interpretable ultrasounds were required to have an angiogram. 12-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 18-month telephone contact: Patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient. 24-month clinic visit: A 2-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events. 36-month clinic visit: A 3-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

A. Study Design

The primary objective of the clinical study was to assess primary patency at 9 months after stenting, where primary patency is defined as uninterrupted (intervention-free) patency since the initial study procedure and patency is defined as < 60% diameter stenosis of the treated segment. Specifically, the primary hypothesis was that the primary patency rate at 9 months on a per-stented artery basis meets the performance goal of 60% (i.e., > 60%). Secondary analyses included MAEs (defined as device- or procedure-related death, Q-wave MI, clinically-driven target lesion revascularization, and significant embolic events), technical success, acute procedural success, 30-day clinical success, target lesion revascularization, blood pressure-related outcomes (i.e., systolic and diastolic blood pressure, number and dosage of anti-hypertensive medications, and improved and cured hypertension); and renal function outcomes (measured by eGFR).

The REFORM study was a prospective, multi-center, single arm study conducted in the United States. 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, or flow-limiting dissection) for *de novo* or restenotic renal artery lesions (≤ 18 mm length) due to atherosclerosis originating within 10 mm of the renal ostium and a reference vessel diameter of 4 to 7 mm. Two lesions, one per side, were allowed per patient. Patients were excluded from the study if they met any of the following conditions: only one functioning kidney, past nephrectomy, kidney transplant, on hemodialysis, or advanced renal disease (e.g., kidney length < 8 cm, serum creatinine ≥ 3.0 mg/dl). Follow-up included post-procedure angiography and ultrasound imaging, and ultrasound (angiography, if ultrasound was uninterpretable) at 9 months. Clinical assessments (e.g., blood chemistry, blood pressure, assessment of anti-hypertensive medications) were scheduled for 1, 9, 24, and 36 months. Telephone contacts were scheduled for 6, 12, and 18 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. An independent clinical events committee (CEC) adjudicated the major adverse events of death, Q-wave MI, and significant embolic events (defined as unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or kidney failure) with respect to their relationship to the device or procedure.

The primary endpoint was evaluated according to the hypothesis that renal arteries treated with the Formula™ Balloon-Expandable Stent will have a primary patency rate at 9 months on a per-stented artery basis that meets a performance goal of 60% derived from published literature on PTRA. The hypothesis was formulated as follows:

Null Hypothesis: the 9-month primary patency rate, γ, is less than or equal to 60%. (Interpretation: the primary patency rate does not meet a performance goal of 60%.)

Ho: $\gamma \leq 60\%$

Alternative Hypothesis: the 9-month primary patency rate, γ, is greater than 60%. (Interpretation: the primary patency rate meets a performance goal of 60%.)

Ha: $\gamma > 60\%$.

A confidence interval for the primary patency rate at 9 months (on a per-stented artery basis) was developed from a Generalized Estimating Equation (GEE) model that incorporated the possibility of bilateral treatment. No covariates were included in the model to test the primary hypothesis.

i. Clinical Inclusion and Exclusion Criteria

The inclusion criteria for the REFORM study were as follows:

- Patient has up to two documented stenotic atherosclerotic lesions of the renal arteries, up to one on each side.
- Stenosis before PTRA, defined as:
  - > 70% by angiography, or
  - Translesional pressure gradient ≥ 20 mmHg systolic or ≥ 10 mmHg mean utilizing a ≤ 4 Fr catheter or pressure wire.
- Suboptimal angioplasty, defined as:
  - ≥ 50% residual stenosis,
  - Grade D dissection or any dissection with a significant compromise in lumen flow, or
  - Translesional pressure gradient ≥ 20 mmHg systolic or ≥ 10 mmHg mean utilizing a ≤ 4 Fr catheter or pressure wire.
- Lesion(s) originate within 10 mm of the renal ostium.
- Lesion length(s) ≤ 18 mm (stenotic) in length.
- Renal artery diameter of 4-7 mm.

The exclusion criteria for the REFORM study were as follows:

- Patient is unwilling to sign and date the informed consent.
- Patient does not agree to return for clinical status assessment at 1 month, 9 months, 24 months, and 36 months and for a non-invasive ultrasound at 9 months.
- Patient does not agree to be contacted by telephone at 6 months, 12 months, and 18 months to assess clinical status.
- Age less than 18 years.
- Pregnant, breast-feeding, or planning to become pregnant in the next 36 months.
- Simultaneously participating in another investigational drug or device study or the patient has completed the follow-up phase for the primary endpoint of any previous study less than 30 days prior to enrollment in this study.
- Patient has any surgical or interventional procedure 30 days prior to the study procedure or intends to have a surgical or interventional procedure within 30 days of the study procedure.

- History of bleeding diathesis, coagulopathy, or will refuse blood transfusions.
- Known hypersensitivity or contraindication to anticoagulation therapy, aspirin, clopidogrel, stainless steel, or contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated.

Anatomic/Angiographic Exclusion Criteria:

- Occluded target or contralateral renal artery.
- Multiple ipsilateral lesions of the target renal artery.
- Untreated, angiographically evident thrombus in the target lesion.
- Lesions located within or beyond a bypass graft.
- Pole to pole distance of affected kidney of 8 cm or less.
- NYHA Class IV at the time of study enrollment.
- Previous kidney transplant.
- Fibromuscular dysplasia.
- Serum creatinine $\geq$ 3.0 mg/dL.
- Patient is on hemodialysis or chronic peritoneal dialysis.
- Previous stent in the artery to be treated.
- Lesions requiring atherectomy.
- Lesion in which any component of the stenosis extends into the arterial branches.
- Known untreated aortic aneurysm > 4 cm.
- History of renal aneurysm (treated or untreated).
- Untreated systemic or local infection OR infection treated for less than 5 days prior to procedure.
- Patients with only one functioning kidney or past nephrectomy.

ii. Follow-up Schedule

1-month clinic visit: included assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

6-month telephone contact: patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient.

9-month clinic visit with ultrasound: assessments of blood chemistry, blood pressure, antihypertensive medications, adverse events, ultrasound for evidence of stenosis. Patients with non-interpretable ultrasounds were required to have an angiogram.

12-month telephone contact: patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient.

18-month telephone contact: patients were contacted by telephone by the investigative site for clinical evaluation. Up to three attempts were made to contact the patient.

24-month clinic visit: a 2-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

36-month clinic visit: a 3-year office visit includes assessments of blood chemistry, blood pressure, antihypertensive medications, and adverse events.

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 Formula™ Balloon-Expandable Stent will have a primary patency rate at 9 months on a per-stented artery basis that meets a performance goal of 60%. 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 7.

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

Follow-up Visit	Patients Eligible for Follow-up [1]	Percent of Data Available			Events Occurring Before Next Visit		
		Clinical or Telephone	Angiography	Ultrasound	Death	With-drawn	Lost to Follow-up
Procedure	100	100% (100/100)	99% (99/100)	80.0% (80/100)	0	2	0
1-month	98	100% (98/98)	Not Required	Not Required	4	0	2
6-month	92	100% (92/92)	Not Required	Not Required	0	3	0
9-month	89	98.9% (88/89)	11.2% (10/89)[2]	91.0% (81/89)	n/a		

[1] Patients eligible for follow-up = patients eligible for follow-up from preceding visit – (patients dead, withdrawn or lost to follow-up since preceding visit + patients not yet due for follow-up at the specified visit).
[2] The protocol specified angiography during follow-up in cases where 9-month diagnostic ultrasound assessments could not be obtained and in cases of target vessel re-interventions.

C. Study Population Demographics and Baseline Parameters

Patient demographics (Table 8), medical history (Table 9), and baseline lesion characteristics (Table 10 and Table 11) were consistent with patient populations described in published literature of renal stent intervention. The most prevalent co-morbidities were hypertension (97%), hypercholesterolemia (83%), past or current smoker (75%), and

peripheral vascular disease (57%) (Table 9). As assessed by the imaging core lab, the mean lesion length was 7.7 mm, the mean pre-procedure percent diameter stenosis was 57.4%, and the mean post-PTRA percent diameter stenosis was 46.9%.

Table 8: Patient Demographics

Demographic	Value (N = 100 patients)
Sex	
Male	44.0% (44/100)
Female	56.0% (56/100)
Age (years, mean ± SD (range))	72 ± 10 (42 - 92)
Height (inches, mean ± SD (range))	65.2 ± 4.1 (50 - 74)
Weight (lbs, mean ± SD (range))	177.4 ± 33.7 (102 - 290)
Ethnicity	
Caucasian or White	82.0% (82/100)
Black or African American	12.0% (12/100)
Hispanic or Latino	4.0% (4/100)
American Indian or Alaska Native	1.0% (1/100)
Other	1.0% (1/100)
Native Hawaiian or other Pacific Islander	0.0% (0/100)
Asian	0.0% (0/100)

Table 9: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Diabetes	
Total	43.0% (43/100)
Type I	2.0% (2/100)
Type II	41.0% (41/100)
Hypercholesterolemia	83.0% (83/100)
Hypertension[1]	
Total	97.0% (97/100)
Pre-hypertension	14.0% (14/100)
Stage 1	31.0% (31/100)
Stage 2	52.0% (52/100)
Stroke/CVA	17.0% (17/100)
Transient Ischemic Attack (TIA)	11.0% (11/100)
Asthma	9.0% (9/100)
Chronic Obstructive Pulmonary Disease (COPD)	19.0% (19/100)
Peripheral Vascular Disease	57.0% (57/100)
Left Ventricular Hypertrophy (LVH)[2]	27.8% (27/97)

Table 9: Medical History

Past or Current Medical Condition	Percent Patients (number/total number)
Rutherford Classification (TASC 2000) [2]	
0: Asymptomatic	67.7% (63/93)
1: Mild Claudication	11.8% (11/93)
2: Moderate Claudication	7.5% (7/93)
3: Severe Claudication	10.8% (10/93)
4: Ischemic Rest Pain	2.2% (2/93)
5: Minor Tissue Loss, Ulceration	0% (0/93)
6: Major Tissue Loss, Gangrene	0% (0/93)
Microalbuminurea	
Yes	8.0% (8/100)
No	52.0% (52/100)
Unknown	40.0% (40/100)
Renal Insufficiency	46.0% (46/100)
Previous Renal Bypass	0% (0/100)
Congestive Heart Failure (CHF)	
Total	26.0% (26/100)
NYHA Class I	6.0% (6/100)
NYHA Class II	6.0% (6/100)
NYHA Class III	3.0% (3/100)
NYHA Class IV	0% (0/100)
Unknown	11.0% (11/100)
Previous Myocardial Infarction (MI)	30.0% (30/100)
Current or Past Smoker	75.0% (75/100)
Current Smoker	14.0% (14/100)

[1] Definitions for hypertension categories:
Pre-hypertension = systolic 120 - 139 mmHg, diastolic 80 - 89 mmHg.
Stage 1 = systolic 140 - 159 mmHg, diastolic 90 - 99 mmHg.
Stage 2 = systolic > 160 mmHg; diastolic > 100 mmHg.
If systolic and diastolic pressures were different categories, the higher category was chosen.

[2] "Unknown" was not an available answer for the LVH and Rutherford Classification questions; patients without available data were removed from the denominator.

Table 10: Baseline Lesion Characteristics

Characteristic	Percent Lesions (number/total number)
Lesion Location	
Right Renal Artery	46.1% (53/115)
Left Renal Artery	52.2% (60/115)
Accessory Right Renal Artery	0.9% (1/115)
Accessory Left Renal Artery	0.9% (1/115)

Table 10: Baseline Lesion Characteristics

Characteristic	Percent Lesions (number/total number)
Previous Renal Intervention	
Yes	0% (0/115)
No ("*de novo*" lesions)	100% (115/115)
Lesion Class	
Ostial	91.3% (105/115)
Non-ostial[1]	8.7% (10/115)
Branch	0% (0/115)
Calcification	
None	37.4% (43/115)
Little	26.1% (30/115)
Moderate	27.0% (31/115)
Severe	9.6% (11/115)
Thrombus	1.7% (2/115)

[1] Non-ostial lesions were defined as lesions originating 5 to 10 mm from the aorta (renal ostium). Lesions originating > 10 mm from the aorta were excluded from the study per the protocol.

Table 11: Baseline Angiographic Data (core lab reported)

Measure	Mean ± SD (range, total lesions)
Lesion Length (mm)	7.7 ± 3.6 (1.7 - 17.1, n = 114)
Pre-procedure	
RVD (mm)	5.3 ± 0.9 (2.7 - 7.4, n = 114)
MLD (mm)	2.2 ± 0.8 (0.3 - 5.6, n = 114)
Percent Diameter Stenosis (%)	57.4 ± 13.8 (22.9 - 94.3, n = 114)
Post-PTRA	
MLD (mm)	2.8 ± 0.8 (1.0 - 5.9, n = 111)
Percent Diameter Stenosis (%)	46.9 ± 13.4 (13.5 - 81.6, n = 111)

D. Safety and Effectiveness Results

i. Safety Results

Major adverse events included procedure- or device-related events of death, Q-wave myocardial infarction (MI), clinically-driven target lesion revascularization (clinically-driven TLR, defined as any angioplasty or bypass surgery performed for thrombosis or >60% diameter stenosis of the originally treated site following the initial procedure in the

presence of clinical symptoms or laboratory evidence indicative of the need for revascularization), and significant embolic events (defined as unanticipated kidney or bowel infarct, lower extremity ulceration or gangrene, or kidney failure). All MAEs, except clinically-driven TLRs, were adjudicated by the CEC. The 9-month MAE rate was 2.2% (two clinically-driven TLRs), demonstrating the safety of the Formula™ stent (Table 12 and Table 13).

Adverse effects that occurred in the PMA clinical study

Table 12: Protocol Defined Major Adverse Events through 9 Months

Major Adverse Event	Number of Events	Percent Patients (number/total number)[1]
30-day Events		
CEC Adjudicated Death	0	0.0% (0/98)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/98)
Clinically-driven Target Lesion Revascularization (TLR)	0	0.0% (0/98)
CEC Adjudicated Significant Embolic Events	0	0.0% (0/98)
Total	0	0.0% (0/98)
9-month Events		
CEC Adjudicated Death	0	0.0% (0/92)
CEC Adjudicated Q-wave Myocardial Infarction (MI)	0	0.0% (0/92)
Clinically-driven Target Lesion Revascularization (TLR)	2	2.2% (2/92)
CEC Adjudicated Significant Embolic Events	0	0.0% (0/92)
Total	2	2.2% (2/92)

[1] Total number = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during the specified time period.

Table 13: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Major Adverse Events			
To 30-days	0	0.0% (0/98)	[0.0%, 3.7%]
Device-related Death[2]	0	0.0% (0/98)	[0.0%, 3.7%]
Index-procedure-related Death	0	0.0% (0/98)	[0.0%, 3.7%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/98)	[0.0%, 3.7%]

Table 13: Protocol Defined Major Adverse Events, Stent Thrombosis, and Hemorrhagic Complications

Event	Number of Events	Percent Patients (number/total number)[1]	95% Confidence Interval
Clinically-driven TLR[3]	0	0.0% (0/98)	[0.0%, 3.7%]
Significant Embolic Events[2]	0	0.0% (0/98)	[0.0%, 3.7%]
From 31 days to 9-months	2	2.2% (2/92)	[0.3%, 7.6%]
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Total	0	2.2% (0/92)	[0.3%, 7.6%]
Device-related Death[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Index-procedure-related Death	0	0.0% (0/92)	[0.0%, 3.9%]
Q-wave Myocardial Infarction[2]	0	0.0% (0/92)	[0.0%, 3.9%]
Clinically-driven TLR[3]	2	2.2% (2/92)	[0.3%, 7.6%]
Significant Embolic Events[2]	0	0.0% (0/92)	[0.0%, 3.9%]
9-Month TLR[3], per lesion	2	2.0% (2/102)	[0.2%, 6.9%]
Stent Thrombosis	0	0.0% (0/97)	[0.0%, 3.7%]
Acute (≤24 hours)	0	0.0% (0/100)	[0.0%, 3.6%]
Sub-acute (>24 hours to ≤30 days)	0	0.0% (0/99)	[0.0%, 3.7%]
Late (>30 days to ≤90 days)	0	0.0% (0/97)	[0.0%, 3.7%]
Hemorrhagic Complication through 30 Days			
Major	2	2.0% (2/99)	[0.2%, 7.1%]
Intracranial hemorrhage	0	0.0% (0/99)	[0.0%, 3.7%]
GI Bleeding	1	1.0% (1/99)	[0.0%, 5.5%]
Bleeding at the access site	1	1.0% (1/99)	[0.0%, 5.5%]
Other Bleeding	0	0.0% (0/99)	[0.0%, 3.7%]
Minor[4]	1	1.0% (1/99)	[0.0%, 5.5%]

[1] Unless otherwise indicated, "Total number" = patients participating in study at end of the time period (i.e., 30 days or 300 days post-procedure) plus discontinued patients who experienced a MAE during the specified time period.
[2] CEC Adjudicated
[3] Target Lesion Revascularization
[4] Any bleeding which does not require >1 unit packed red blood cells

ii. Effectiveness Results

One hundred twenty-two (122) Formula™ stents were placed to treat 115 renal artery lesions. Most lesions (93.0%) were treated with single stents. By core lab assessment, the mean post-procedure percent diameter stenosis was 8.5% (Table 14), and residual diameter stenosis of < 30% was seen in 95.6% (109/114) of lesions. Therefore, the Formula™ stent was effective in establishing patency at the conclusion of the procedure.

Table 14: Post-Procedure Angiographic Data (core lab reported)

Measure	Mean ± SD (range, total lesions)
Post-procedure	
MLD (mm)	4.8 ± 0.8 (2.6 - 6.5, n = 114)
Percent Diameter Stenosis (%)	8.5 ± 13.2 (-41.6 - 44.6, n = 114)

Primary Endpoint
The 9-month primary patency rate met the performance goal. The 9-month primary patency rate was 91.7% and the lower limit of the 95% two-sided confidence interval is 84.2%; the latter is greater than the performance goal of 60% ($p < 0.0001$). These results demonstrate the effectiveness of the Formula™ stent in treating atherosclerotic lesions of the renal arteries following suboptimal angioplasty.

Secondary Endpoints
Secondary endpoint analyses included major adverse events (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, and improved or cured hypertension), and renal function (as measured by eGFR).

Device-related success measures ranged from 94.8% to 97.4%. Technical success (successful delivery and deployment of a Formula™ stent), acute procedural success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs before discharge), and 30-day clinical success (< 30% residual stenosis post-procedure by core lab analysis and no MAEs within 30 days) outcomes are summarized in Table 15. These results support the safety and effectiveness of the Formula™ stent in establishing renal artery patency.

Table 15: Device-related Success Measures

Measure	Analysis Percentage (number/total number)	
	Per Patient	Per Lesion
Technical Success	97.0% (97/100)	97.4% (112/115)
Acute Procedural Success	94.9% (94/99)	95.6% (109/114)
30-day Clinical Success	94.8% (92/97)	95.5% (106/111)

Blood pressure-related outcomes demonstrated significantly decreased systolic blood pressure from pre-procedure to 9-month follow-up ($p = 0.003$) and that most patients (85%) were taking the same number or fewer anti-hypertensive medications at 9 months (

Table **16** and Table 17, respectively). These data demonstrate the clinical utility of the Formula™ stent and suggest that revascularization with the Formula™ stent does not adversely affect blood pressure outcomes.

Table 16: Blood Pressure Results

Blood Pressure	Mean ± SD (range, total patients)	
	Systolic (mmHg)	Diastolic (mmHg)
Pre-procedure	150.3 ± 20.6 (102 - 202, n = 100)	73.9 ± 12.9 (43 - 112, n = 100)
1 Month	137.9 ± 18.7 (96 - 195, n = 98)	72.9 ± 12.2 (46 - 115, n = 98)
9 Months	140.5 ± 21.0* (97 - 203, n = 87)	77.5 ± 12.9 (51 - 122, n = 87)
Change at 9 Months from Pre-procedure (Bonferroni adjusted 95% two-sided confidence interval)	[-16.5, -2.7], n = 87	[-0.3, 7.4], n = 87

*$p = 0.003$ compared to pre-procedure systolic blood pressure (Bonferroni adjusted p-value).

Table 17: Anti-hypertensive Medication Results

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number Per Patient	
Pre-procedure	2.7 ± 1.2 (0 - 6, n = 100)
1 Month	2.6 ± 1.2 (0 - 5, n = 98)
9 Months	2.5 ± 1.1 (0 - 5, n = 87)

Table 17: Anti-hypertensive Medication Results

Anti-hypertensive Medications	Mean ± SD (range, total patients)
Number of Medications at 9 Months *(change from pre-procedure)*	
Decrease	23.0% (20/87)
No Change	62.1% (54/87)
Increase	14.9% (13/87)
Dose of Medications at 9 Months *(change from pre-procedure)*	
Decrease	29.9% (26/87)
No Change	42.5% (37/87)
Increase	27.6% (24/87)

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 (Table 18), further demonstrating the clinical utility of the Formula™ stent and suggesting that revascularization with the Formula™ stent does not adversely affect renal function.

Table 18: Renal Function Results

Measure	Mean ± SD (range, total patients)
Serum Creatinine (mg/dl)	
Pre-procedure	1.3 ± 0.5 (0.5 - 2.9, n = 100)
1 Month	1.3 ± 0.4 (0.6 - 2.5, n = 94)
9 Months	1.3 ± 0.4 (0.5 - 2.7, n = 84)
eGFR (ml/min) [1]	
Pre-procedure	60.7 ± 28.8 (15.1 - 179.3, n = 100)
1 Month	59.3 ± 25.3 (14.8 - 147.5, n = 94)
9 Months	60.6 ± 27.7 (22.1 - 168.5, n = 84)
Change in eGFR Per Patient at 9 Months from Pre-procedure (Bonferroni adjusted 95% two-sided confidence interval)	[-3.3, 3.6], n = 84

[1] eGFR was calculated based on the Cockcroft-Gault equation. For men, eGFR (ml/min) = (140 - age) × weight (kg) / (72 × S_{cr}), where S_{cr} is serum creatinine (mg/dl). For women eGFR (ml/min) = (140 - age) × weight (kg) × 0.85 / (72 × S_{cr}). Note: If patient weight was not available at follow-up the patient's most recent weight was substituted.

iii. Subgroup Analyses

Gender was evaluated for potential association with the outcome of patency, as seen in Table 19. The data indicate that gender does not affect the incidence of patency.

Table 19: Patency by Gender

Gender	Percent Patency (number/total number)	
	Per Subject	Per Lesion
Male	90.5 (38/42)	91.7 (44/48)
Female	90.9 (40/44)	92.2 (47/51)

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 device are based on data collected in a clinical study conducted to support PMA approval as described above. The major adverse event rate, defined as procedure- or device-related events of death, Q-Wave MI, clinically driven target lesion revascularization (TLR), and significant embolic events (defined as unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene, or kidney failure) was 2.2%.

Comprehensive preclinical bench testing was performed on the Formula™ Balloon-Expandable 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 Formula™ Balloon-Expandable Renal Stent System met its performance and design specifications.

Preclinical *in vivo* animal testing was conducted on 15 animals in order to evaluate the acute and chronic performance of the Formula™ Balloon-Expandable Renal Stent System. The studies were performed to evaluate deployment and histopathological response in swine models for up to 30 days. The results support the safety and expected performance of the Formula™ Balloon-Expandable Renal Stent System.

Biocompatibility testing was performed on the Formula™ Balloon-Expandable 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 Formula™ Balloon-Expandable Renal Stent System. The testing demonstrated that the Formula™ Balloon-Expandable Renal Stent System maintains a Sterility Assurance Level of 10^{-6}. The results of shelf life testing confirmed that the Formula™ Balloon-Expandable Renal Stent System maintains functionality throughout its 3-year shelf life, and the packaging testing demonstrated that the packaging adequately protects the device throughout its 3-year shelf life.

B. Effectiveness Conclusions

Results of the REFORM study demonstrate the safety and effectiveness of the Formula™ Balloon-Expandable Renal Stent in the treatment of *de novo* or restenotic renal artery lesions due to atherosclerosis (≤ 18 mm length) originating within 10 mm of the renal ostium and with a reference vessel diameter of 4 to 7 mm following suboptimal angioplasty, which was defined as ≥ 50% residual stenosis, ≥ 20 mmHg systolic or ≥ 10 mmHg mean translesional pressure gradient, or flow-limiting dissection.

Specifically, the 9-month patency rate (91.7%) exceeded the performance goal of 60%, and use of the Formula™ stent was associated with a low MAE rate, high technical and procedural success rates, improvement in hypertension, and maintenance of renal function.

C. Overall Conclusions

The results of the REFORM study provide a reasonable assurance of the safety and effectiveness of the Formula™ Balloon-Expandable Renal Stent System in the treatment of *de novo* or restenotic renal artery lesions due to atherosclerosis (≤ 18 mm length) originating within 10 mm of the renal ostium and with a reference vessel diameter of 4 to 7 mm following suboptimal angioplasty. The data presented formed the basis for FDA's finding that the Formula™ Balloon-Expandable Renal Stent System is safe and effective for its intended use.

XIV. CDRH DECISION

FDA issued an approval order on January 14, 2010. As a condition of PMA approval, the sponsor is required to follow the existing 100-patient REFORM 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