

The packaging materials and sterilization process for the PALMAZ Balloon-Expandable Medium Stents (Models P104R, P154R and P204R) are identical to the packaging materials and sterilization process used for the PALMAZ Balloon-Expandable Stent Model P308 approved under P890017. Therefore, no additional packaging or shelf-life testing were required for the PALMAZ Balloon-Expandable Stent sizes that are the subject of this submission.

The packaging and shelf-life testing that established the current five-year expiration date for the PALMAZ Balloon-Expandable Stent Model P308, also supports the five-year expiration date for the PALMAZ Balloon-Expandable Medium Stents. Please refer to the SSED of the original PMA P890017.

Expiration dating of the POWERFLEX Plus delivery catheter is based on the accelerated aging study conducted on the POWERFLEX PTA Catheter cleared for marketing under K971516, as well as accelerated aging testing conducted on the POWERFLEX Plus delivery catheter. Except for the marker band, all materials used in the construction of the POWERFLEX Plus delivery catheter were also used in the construction of the POWERFLEX PTA Catheter. Therefore, the results of the accelerated aging are applicable to the POWERFLEX Plus delivery catheter.

The results of the visual, dimensional, and functionality testing on the accelerated aged POWERFLEX PTA Catheter and the marker band bond strength testing on the accelerated aged POWERFLEX Plus delivery catheter support the three-year expiration date.

9.4 Animal Testing

A porcine animal study was conducted to evaluate the procedural steps of deploying the Palmaz Medium Stent in arteries with diameters similar to those of human arteries. A total of 29 Palmaz stents were implanted in the iliac or femoral arteries of 4 pigs. The study results showed that the Palmaz stent could be successfully crimped on the balloon catheter and deployed at the intended site within the artery.

10. Summary of Clinical Studies

A feasibility study (ASPIRE) was conducted to evaluate the safety and deliverability of the PALMAZ Balloon-Expandable Stent design in treating proximal renal artery stenosis. A total of 51 patients (N = 63 lesions), at seven investigation centers in the United States, with de novo or restenotic renal artery lesions located in vessels that had a $\geq 70\%$ stenosis, reference vessel diameter of 4 to 7 mm were treated with the PALMAZ Balloon-Expandable Stent. The mean pre-procedure percent diameter stenosis (N = 60 lesions) of 61.3 ± 14.4 , 95% CI of [57.6, 65.1] decreased to 4.6 ± 8.9 , 95% CI of [2.3, 6.9] post-procedure. At one-year follow-up, the percent diameter stenosis (N = 24 lesions) was 26.9 ± 23.8 , 95% CI of [16.8, 36.9]. There were no in-hospital major adverse events (i.e., death, renal infarct of treated kidney, renal bypass of treated kidney, or revascularization of target lesion). Four deaths and four reports of target lesion revascularization occurred during the two-year follow-up period. The rate of other complications including renal failure, bleeding complications, and vascular complications was 23.5%.

The ASPIRE feasibility study was followed by a multi-center, prospective, non-randomized study (ASPIRE2). The purpose of the ASPIRE2 study was to evaluate the effectiveness and safety of the PALMAZ Balloon-Expandable Stent in patients with atherosclerotic proximal renal artery stenosis that was suboptimally treated with PTRAs, as compared to a pre-specified performance criteria of a 40% nine-month restenosis rate. The study population consisted of 208 patients enrolled at 23 investigational centers in the United States. A total of 252 lesions were treated with one stent placed in 231 lesions and 2 stents placed in 21 lesions. Forty-three patients were treated for bilateral renal artery disease. The ASPIRE2 study is summarized below.

Study Endpoints: The primary endpoint was the restenosis rate at 9-months, determined by duplex ultrasound. Secondary endpoints included:

- Acute procedural success defined as <30% residual stenosis immediately after stent deployment as determined by the Core Laboratory (if no quantitative angiographic analysis was available, visual estimates were used) and = 5 mm Hg residual translesion.
- Worsening renal function defined by a rise in serum creatinine at 30 days, 6 months, 9 months and 24 months:
 - If baseline level is = 2.0 mg/dl, a = 50% increase in serum creatinine.
 - If baseline level is > 2.0 mg/dl, a 1 mg % increase in serum creatinine.
- Blood pressure measurement change / antihypertensive medication at 30 days, 6 months, 9 months and 24 months: cured, improved, no improvement or censored.
- Absence of major adverse events at 30 days, 3 months, 6 months, 9 months and 24 months:
- Incidence of device or procedure-related death, procedure related Q-wave myocardial infarction, target lesion revascularization (TLR) or significant embolic events (defined as end-organ damage, e.g., unanticipated kidney/bowel infarct, ulcerated or gangrenous foot).

An independent clinical events committee adjudicated all of the major adverse events (MAEs) and other events. Endpoints were analyzed on an intent-to-treat basis.

Patients Studied: Eligible patients had either de novo or restenotic renal artery lesions with a = 70% stenosis, a reference vessel diameter of 4 to 8 mm located within 10 mm of the aorta and suboptimally treated with PTRAs. Patients with a total occlusion of the renal artery or having advanced renal disease as evidenced by serum creatinine of = 3.0 mg/dl or kidney length of < 8 cm were excluded from the study. Baseline characteristics for the patients in the ASPIRE2 study are presented in Table 3.

Table 3. Baseline Characteristics (N = 208 patients, 252 lesions)

Characteristic	
Age (yrs), mean ± SD (N)	69.6 ± 9.9 (208)
Number of men	36.5% (76/208)
History of smoking	67.8% (141/208)
History of coronary artery disease	38.5% (80/208)
History of diabetes mellitus	26.0% (54/208)

Atherosclerotic peripheral vascular disease (other than renal artery stenosis)	44.2% (92/208)
Reference vessel diameter (mm), mean \pm SD(N)	4.83 \pm 1.09 (244)
Minimum lumen diameter (mm), mean \pm SD(N)	1.84 \pm 0.75 (244)
Lesion length (mm), mean \pm SD (N)	6.54 \pm 3.23 (242)
Percent diameter stenosis, mean \pm SD (N)	61.5 \pm 13.8 (244)

Methods: Patients eligible for the study underwent a PTRA on a single renal artery and had an angiographically documented suboptimal result defined by the presence of unfavorable lesion morphology consisting of one or more of the following: an inadequate angiographic result as defined by a \geq 50% lumen diameter narrowing; a 20 mm Hg peak translesion pressure gradient; a 10 mm Hg or greater mean translesional pressure gradient; and Grade D dissection or any dissection with significant compromise in lumen flow. Patients were to be treated with no more than two stents per renal artery. Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Clinical follow-up visits were conducted at 30 days, 6 months and 9 months post-procedure. Baseline quantitative angiography was performed pre-procedure, post-PTRA, and post-procedure in all patients. Duplex Ultrasound was utilized to make an initial determination of restenosis at the 9-month follow-up. If restenosis was observed by Duplex Ultrasound, a confirmatory angiogram was performed to document the amount of restenosis present. Computer assisted quantitative angiographic analysis (QA) and Duplex Ultrasound were performed at central laboratories.

ASPIRE2 Study Results: In suitable patients, stent placement in renal arteries following failed angioplasty resulted in improved acute angiographic outcomes and a nine month restenosis rate of 17.4%, 95% CI of [11.9%, 21.9%]. Clinical follow-up was available on 93.3% (194/208) and angiographic and/or duplex ultrasound follow-up was available on 73.6% (153/208) of patients at 9 months (270 \pm 30 days). The major adverse event rate (defined as device or procedure related death, Q-wave myocardial infarction, target lesion revascularization, or significant embolic event) at 270 days was 9.6%, 95% CI of [6.0%, 14.5%]. Freedom from target lesion revascularization at 270 days was 95.5% with 95% CI of [93.0%, 98.0%]. The principal effectiveness and safety results are presented in Table 4. The freedom from major adverse events Kaplan-Meier curve is presented in Figure 1.

The ASPIRE2 study included 43 patients who had a contralateral renal artery lesion treated with the PALMAZ Stent. The patients with bilateral stenosis had the most significant lesion treated with PTRA first. If the results were suboptimal, the lesion was treated with a stent and the patient was enrolled into the study. Treatment of the contralateral lesion involved PTRA and stent placement, or primary stenting of the lesion. Stent placement in the patients who had both renal arteries treated resulted in a nine month restenosis rate of 16.8%, 95% CI of [7.8%, 26.0%] with a 270-day major adverse event rate of 14.0% with 95% CI of [6.3%, 25.7%]. Freedom from target lesion revascularization at 270 days for the patients treated bilaterally was 97.5% with 95% CI of [94.2%, 100.0%]. The lesion-based endpoint values for patients with bilateral lesions may not be independent, and therefore may be correlated. The effectiveness measures presented herein from the ASPIRE2 study were not based upon the analysis of correlated lesion data, but rather the analysis of independent lesion data. Statistical comparisons between the unilateral and bilateral stented patients revealed no consistent pattern of difference in response to stenting between the two groups.

A twenty-four month follow-up visit was conducted to obtain blood pressure measurements, hematology evaluations and the recording of adverse events. The twenty-four month clinical safety and effectiveness data obtained on the 208 patients enrolled in the ASPIRE2 Study is presented in Table 4. There were a total of 41 major adverse events reported for the 208 patients and consisted of the following: one device or procedure related death, 30 target lesion revascularizations and 10 significant embolic events. Freedom from target lesion revascularization at 720-days was 85.9% with 95% CI of [81.4%, 90.4%]. The mean serum creatinine level at twenty-four months (N = 153 patients) was 1.46 mg/dl \pm 0.81 mg/dl, 95% CI of [1.33, 1.58]. The mean systolic and diastolic blood pressure at twenty-four months (N = 158 patients) was 149.3 mm Hg \pm 25.3 mm Hg, 95% CI of [145.3, 153.2] and 76.9 mm Hg \pm 11.9 mm Hg, 95% CI of [75.0, 78.7], respectively. The mean number of antihypertensive medications reported taken by the patients at twenty-four months (N = 182 patients) was 2.30 \pm 1.26, 95% CI of [2.1, 2.5].

The percentage of female to male distribution (63.5% versus 36.5%) in the ASPIRE2 study was higher than that reported in the literature. Analysis of the safety and effectiveness measures found that only post-procedure percent stenosis and post-procedure minimum lumen diameter

demonstrated a statistically significant advantage for females. Women averaged 3.1% less in-lesion stenosis (p=0.0328) and 7.2% less in-stent stenosis compared to males (p=0.0019). Similarly, women averaged 0.3mm greater in-lesion MLD (p=0.0036) and 0.2mm greater in-stent MLD compared to male patients (p=0.0793). However, follow-up out to nine-months showed no statistical differences in the restenosis rate or freedom from target lesion revascularization between males and females.

Table 4. Principal Effectiveness And Safety Results

Effectiveness Measures – Lesions	All Lesions (N=252)	95% C.I.
Acute Procedure Success	80.2% (182/227)	[74.4%, 85.2%]
Post-Procedure in-lesion % DS	10.26 ± 11.1 (244)	(8.86, 11.67)
Range (min, max)	(-35.3, 61.31)	
Post-Procedure in-stent % DS	-2.17 ± 17.5 (243)	(-4.39, 0.05)
Range (min, max)	(-86.8, 54.24)	
Post-Procedure in-lesion MLD	4.31 ± 0.98 (244)	(4.19, 4.43)
Range (min, max)	(1.62, 6.89)	
Post-Procedure in-stent MLD	4.87 ± 1.07 (243)	(4.74, 5.01)
Range (min, max)	(1.89, 8.50)	
9 Month Restenosis Rate (Lesion-based)	17.4%% (32/184)	[11.9%, 21.9%]
TLR-free at 270 Days (Lesion Based, K-M)	96.7%	[94.5%, 98.9%]
Primary Patency (QA/Duplex Ultrasound)	81.0% (149/184)	[74.6%, 86.4%]
Primary Patency (Clinical)	96.8% (244/252)	[93.8%, 98.6%]
Secondary Patency (QA/Duplex Ultrasound)	82.6% (152/184)	[76.3%, 87.8%]
Secondary Patency (Clinical)	99.2% (250/252)	[97.2%, 99.9%]
Effectiveness Measures – Patients	All Patients (N=208)	95% C.I.
Average Systolic Blood Pressure (mmHg)		
Baseline	167.6 ± 25.2 (208)	[164.2, 171.0]
9 Months*	149.1 ± 24.0 (178)	[145.6, 152.6]
24 Months*	149.3 ± 25.3 (158)	[145.3, 153.2]
Average Diastolic Blood Pressure (mmHg)		
Baseline	81.5 ± 13.1 (208)	[79.8, 83.3]
9 Months*	77.3 ± 12.1 (178)	[75.5, 79.0]
24 Months*	76.9 ± 11.9 (158)	[75.0, 78.7]
Average Number of Antihypertensive Medications		
Baseline	2.8 ± 0.9 (208)	[2.7, 3.0]
9 Months*	2.4 ± 1.2 (196)	[2.2, 2.6]
24 Months*	2.3 ± 1.3 (182)	[2.1, 2.5]
Safety Measures – Patients	All Patients (N=208)	95% C.I.
In-hospital Major Adverse Events	1.4% (3/208)	[0.3%, 4.2%]
Out-of-hospital Major Adverse Events to 9 Months	8.2% (17/208)	[4.8%, 12.8%]
In-hospital and Out-of-hospital MAEs to 9 Months	9.6% (20/208)	[6.0%, 14.5%]
MAE-free at 270 days (K-M)	90.3%	[88.2%, 94.4%]
In-hospital and Out-of-hospital MAEs to 24 Months	19.7% (41/208)	[14.5%, 25.8%]
Stent Thrombosis (9 Months)	1.0% (2/208)	[0.1%, 3.4%]
CVA (9 Months)	0.0% (0/208)	[0.0%, 1.8%]
Major Bleeding (9 Months)	1.4% (3/208)	[0.3%, 4.2%]
Major Vascular (9 Months)	4.8% (10/208)	[2.3%, 8.7%]
Average Serum Creatinine Level (mg/dl)		

Baseline	1.36 ± 0.52 (207)	[1.29, 1.43]
9 Months	1.40 ± 0.61 (173)	[1.30, 1.49]
24 Months	1.46 ± 0.81 (153)	[1.33, 1.58]

Numbers are % (count/available field sample size) Mean ± Standard Deviation or Range (Min,Max).

CI – Confidence Interval

*P-value of <.001 for the test for difference of means between each time point and baseline, based on paired t-test.

Acute Procedure Success - Acute procedure success was defined as angiographic success of < 30% residual stenosis as determined by the Core Laboratory (if no QA, visual estimates were used), and ≤ 5 mmHg mean residual gradient.

Restenosis - ≥ 50% diameter stenosis by QA at 9 month follow-up or if QA not available then renal to aortic ratio within the stent of 3.5 or greater or an absolute peak systolic velocity within the stent greater than 200 cm/sec via duplex ultrasound.

TLR-free at 270 Days - No target lesion revascularization within 270 Days using Kaplan-Meier estimates.

Primary Patency (Angiographic or Duplex Ultrasound) - < 50% diameter stenosis by QA at 9 month follow-up or if QA not available then a renal to aortic ratio within the stent of less than 3.5 and an absolute peak systolic velocity within the stent less than 200 cm/sec via duplex ultrasound performed 9 months post-study procedure without any reintervention.

Secondary Patency (Angiographic or Duplex Ultrasound) - < 50% diameter stenosis by QA at 9 month follow-up or if QA not available then a renal to aortic ratio within the stent of less than 3.5 and an absolute peak systolic velocity within the stent less than 200 cm/sec via duplex ultrasound performed 9 months post-study procedure with or without repeat percutaneous reintervention.

Primary Patency (Clinical) – No target lesion revascularization through last follow-up.

Secondary Patency (Clinical) - No repeated target lesion revascularization through last follow-up.

Major Adverse Event (MAE) - The following procedure or device related events were considered to be major adverse events:

-death

-Q-wave myocardial infarction

-target lesion revascularization

-loss of kidney function or significant embolic events

** - Major Adverse Events were adjudicated by the Clinical Events Committee

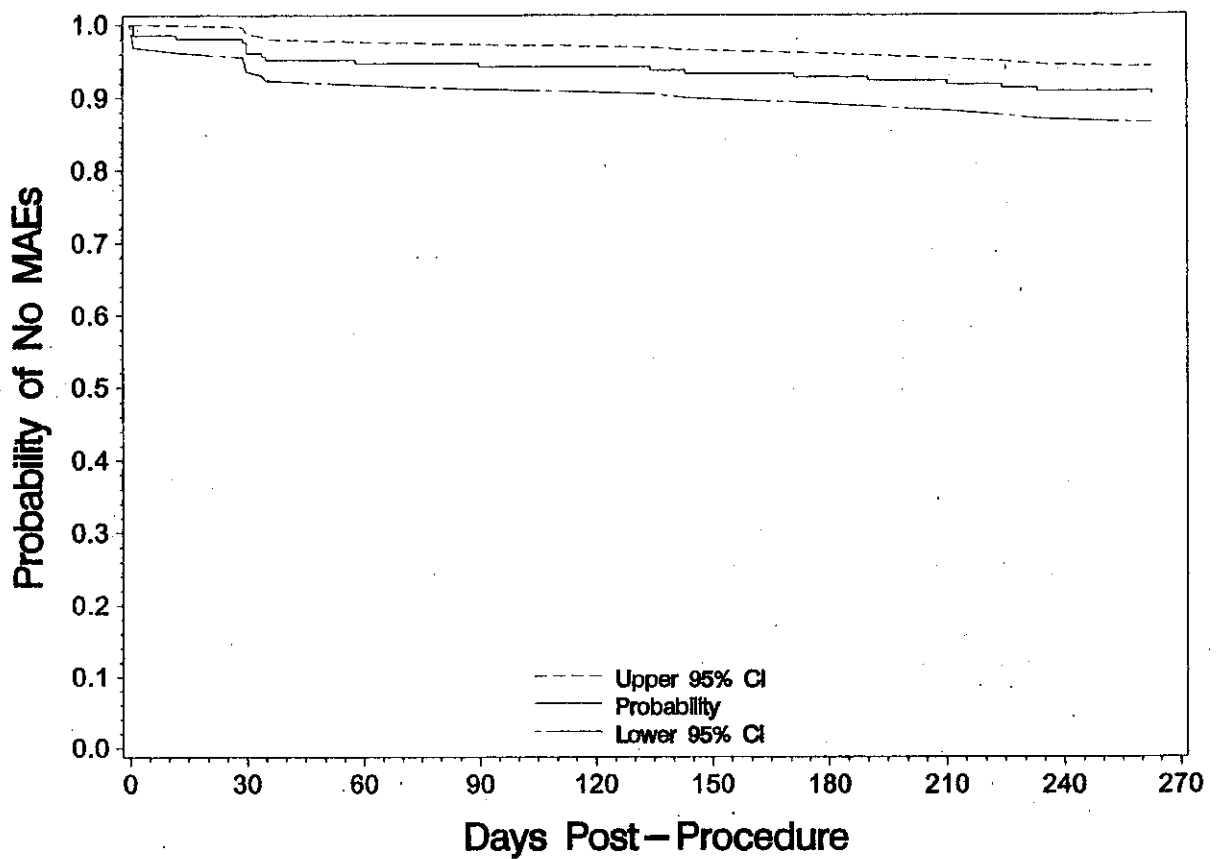
Stent Thrombosis - After successful stent deployment, angiographic thrombus within the stented vessel during the first 30 days following stent deployment.

CVA - Acute neurological deficits recorded by the clinical sites.

Major Bleeding - Transfusion of blood products due to blood loss resulting from the percutaneous revascularization procedure, or blood loss resulting in change in anticoagulation regimen.

Major Vascular - Occurrence of hematoma, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure related transfusion, or vascular surgical repair.

Figure 1. Freedom from Major Adverse Events (To 270 Days):
All Patients (N=208)



Days Post-Procedure	0	Discharge	30	180	270
# Entered	208	208	204	195	182
# Censored	0	0	3	5	180
# At risk	208	208	204	192	177
# Events	0	4	8	6	2
# Events/Month		10	2.7	0.8	0.2
% Survived	100	98.1	94.2	91.3	90.3
SE		1	1.6	2	2.1

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the PALMAZ Balloon-Expandable Stent meets or exceeds safety and performance specifications.

Multicenter clinical data found that the nine-month restenosis rate (primary effectiveness endpoint) for the PALMAZ Balloon Expandable Stent was lower than the pre-specified objective performance criterion of > 40 percent. Key secondary effectiveness endpoints such as blood pressure reduction and number of antihypertensive medications were positively affected. In addition, no significant safety concerns were noted with placement of the stent. Acute procedure success rate was acceptable and major adverse event rates, both in and out of hospital, occurred at expected frequencies.

The results of the multi-center clinical investigation show that that the PALMAZ Balloon-Expandable Stent is reasonably safe and effective for the treatment of patients with atherosclerotic renal artery stenosis following suboptimal percutaneous renal angioplasty (PTRA) of a *de novo* or restenotic lesion when used in accordance with the directions for use.

12. Panel Recommendation

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 System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

15. FDA Decision

The FDA issued an approval order on July 10, 2002.

In addition to the General Conditions of Approval, all patients enrolled in the ASPIRE2 study are to be followed out to three years after implant of the Palmaz stent.

The applicant's manufacturing facility was found to be in compliance with the Quality System Regulation (Part 820).

14. Approval Specifications

Instructions for Use (see the 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.



CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

Instructions for Use
PALMAZ® Balloon Expandable Stent for the Renal Arteries

STERILE. The PALMAZ® Balloon Expandable Stent and crimping tube are sterilized with gamma radiation. Nonpyrogenic. The stent is radiopaque. For single use only. Do not autoclave.

IMPORTANT: The crimping tube packaged with the PALMAZ Stent is not compatible with the POWERFLEX® Plus PTA Catheter.

NON-STERILE. The crimping tool and introducer tube, *provided separately*, are supplied **NON-STERILE** and must be sterilized prior to use. The crimping tool and introducer tube should be sterilized by autoclaving in accordance with hospital procedures.

DEVICE NAME

The device brand name is the PALMAZ® Balloon Expandable Stent.

1.0 DEVICE DESCRIPTION

The PALMAZ® Balloon-Expandable Stent is a 316L stainless steel, slotted tube which is expanded with the use of the recommended delivery systems (refer to Table 1).

The delivery system, the POWERFLEX® PLUS PTA Catheter, consists of a dual lumen shaft design with a distal inflatable balloon. Two radiopaque marker bands indicate the dilating section of the balloon.

Available Stent Lengths (mm):	10, 15 and 20.
Expanded Stent Diameters (mm):	4, 5, 6, 7 and 8 (determined by the diameter of the fully inflated delivery catheter).
Stent Material:	Electropolished stainless steel (316L), cut from seamless tubing.
Stent Geometry:	14 circumferential rows of slots. Slotted tube pattern.
Nominal Stent Foreshortening:	1.5 mm or less for the 10 mm length stent. 2.3 mm or less for the 15 mm length stent. 3.1 mm or less for the 20 mm length stent.

Delivery System Usable Length: 40 cm, 65 cm, 80 cm, 110 cm and 135 cm (Not all recommended balloon catheter sizes are sold in all catheter lengths.)

Recommended Delivery Balloon: The PALMAZ® Balloon-Expandable Stent is sold unmounted for use with the Cordis POWERFLEX® PLUS PTA Catheter. A plastic crimping tube is also provided with the stent.
IMPORTANT: When using the POWERFLEX® PLUS balloon catheter, use the crimping tube that is packaged with the balloon, NOT the Stent. The crimping tube supplied with the Stent is NOT compatible with the POWERFLEX® PLUS balloon catheter.

Nominal Balloon Inflation Pressure: 10 atm (1013 kPa)

Recommended Cordis Catheter Sheath Introducer: 6F (2.0 mm) with 4 – 6 mm POWERFLEX® PLUS.
 7F (2.3 mm) with 7 & 8 mm POWERFLEX® PLUS

Table 1

Stent Description		Stent Lengths		POWERFLEX® PLUS	Recommended Cordis Catheter Sheath Introducer (CSI) and Guiding Catheter	
Product Code	Nominal Dia (mm)	Unexpanded (mm)	Expanded (mm)	Catalog Number	CSI Size French	Guiding Catheter Size French
P104R	4	10.0	9.9	412-4010	6F	8F
	5	10.0	9.7	412-5010	6F	8F
	6	10.0	9.4	412-6010	6F	8F
	7	10.0	9.0	412-7010	7F	9F
	8	10.0	8.5	412-8010	7F	9F
P154R	4	15.0	14.8	412-4015	6F	8F
	5	15.0	14.5	412-5015	6F	8F
	6	15.0	14.0	412-6015	6F	8F
	7	15.0	13.4	412-7015	7F	9F
	8	15.0	12.6	412-8015	7F	9F
P204R	4	20.0	19.7	412-4020	6F	8F
	5	20.0	19.3	412-5020	6F	8F
	6	20.0	18.7	412-6020	6F	8F
	7	20.0	17.8	412-7020	7F	9F
	8	20.0	16.8	412-8020	7F	9F

Use Cordis Crimping Tool CRT20 and Introducer Tube INTR4 for all product codes and lengths.

French size conversions: 6F (2.0mm), 7F (2.3mm), 8F (2.7mm), 9F (3.0mm)

¹ Catheter suffices for the POWERFLEX PLUS refers to the usable catheter length. Any of the following catheter length suffixes may be used: T (40cm), V (65cm), S (80cm), L (110cm) and X (135cm). NOTE: Not all balloon sizes are sold in all catheter lengths.

2.0 INDICATION FOR USE

The PALMAZ® Balloon-Expandable Stent is indicated for use in patients with atherosclerotic disease of the renal arteries following suboptimal percutaneous renal angioplasty (PTRA) of a de novo or restenotic lesion (≤ 22 mm in length) located within 10 mm of the aortorenal artery border and with a reference vessel diameter of ≥ 4 mm and ≤ 8 mm. Suboptimal PTRA results are defined by one or more of the following unfavorable results.

- 1) $\geq 50\%$ residual stenosis by visual estimate
- 2) ≥ 20 mmHg peak translesional pressure gradient
- 3) ≥ 10 mmHg mean translesional pressure gradient
- 4) Grade D dissection (a spiral shaped filling defect within the lumen of the vessel) or any dissection with significant compromise in lumen flow

3.0 CONTRAINDICATIONS

The PALMAZ Balloon-Expandable Stent is contraindicated for use in patients who have a lesion that cannot be crossed with a wire and/or balloon catheter.

4.0 WARNINGS

1. The stent and delivery balloon should be used only by physicians trained in interventional techniques such as percutaneous transluminal angioplasty (PTA) and placement of intravascular stents.
2. Persons with bleeding diathesis or uncontrollable hypercoagulability are not suitable candidates for stent implantation.
3. Persons with lesions in arteries to transplanted or bypassed kidneys are not suitable candidates for stent implantation.
4. The long-term outcome following repeat dilatation of endothelialized stents is unknown at present.
5. Persons with allergic reactions to stainless steel or its components (for example, nickel) may suffer an allergic response to this implant.
6. Caution should be taken with patients with poor renal function who, in the physician's opinion, may be at risk for a contrast medium reaction. Note: Patients with serum creatinine ≥ 3.0 mg/dl were excluded from the ASPIRE2 clinical study. (See Section 7, Clinical Study Information.)
7. The stent may cause a thrombus, distal embolization, or may migrate from the site of implant down the arterial lumen. Appropriate sizing of the vessel is required to reduce the possibility of stent migration. In the event of thrombosis of the expanded stent, thrombolysis and PTRA should be attempted.
8. Before insertion of the primary dilatation catheter, the appropriate antiplatelet and anticoagulant therapy should be administered. Aspirin may be used as potential antiplatelet therapy. Antiplatelet therapy should be maintained for at least 24 hours prior to the procedure and for at least three months post-procedure.

9. In patients requiring the use of antacids and/or H2 antagonists before or immediately after stent placement, oral absorption of antiplatelet agents (e.g., aspirin) may be adversely affected.

5.0 PRECAUTIONS

Stent Handling Precautions

1. The PALMAZ Balloon-Expandable Stent and Crimping Tube are supplied STERILE. The Stent and Crimping Tube are intended for single use only. Do not resterilize and/or reuse the device.
2. Store in a cool, dry, dark place.
3. Use the PALMAZ Balloon-Expandable Stent prior to the "Use By" date printed on the package.

Stent Placement Precautions

4. When using the POWERFLEX PLUS balloon catheter, use the crimping tube that is packaged with the balloon, NOT with the stent. The crimping tube supplied with the stent is NOT compatible with the POWERFLEX PLUS balloon catheter.
5. Maximum balloon inflation pressure must not exceed the recommended inflation pressure specified on the catheter label.
6. Use of an inflation device with a manometer is recommended during this procedure so as to minimize the risk of over-inflation. Over-stretching of the artery may result in rupture and life threatening bleeding
7. The inflation diameter of the balloon used during stent delivery should approximate the diameter of the dilated lesion and intended arterial implant site.
8. When catheters are in the body, they should be manipulated only under fluoroscopy using radiographic equipment that provides high quality imaging.
9. Circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the stent may cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the recommended balloon catheter, it can be withdrawn and a new balloon catheter exchanged over a guidewire to complete expansion of the stent.
10. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different metals in tandem where overlap or contact is possible, with an exception: stents made of 316L stainless steel are compatible with stents made of nickel titanium alloy.

Post-Stent Placement Precautions

11. As with any type of vascular implant, infection secondary to contamination of the stent may lead to thrombosis, pseudoaneurysm or rupture into a neighboring organ or the retroperitoneum.
12. In the event of complications, such as infections, pseudoaneurysm or fistulization, surgical removal of the stent may be required. Standard surgical procedure is appropriate
13. The stent may cause artifacts with MRI scans due to distortion of the magnetic field. The artifacts caused by the 316L stainless steel stent should not be greater than that caused by surgical metal clips. An MRI scan should not be used until the stent implantation site has had a chance to heal (estimated to be 8 weeks), in order to minimize the risk of migration of the stent under a strong magnetic field.

6.0 ADVERSE EVENTS

6.1 Observed Adverse Events

A total of 51 patients with proximal renal artery disease were evaluated in the ASPIRE (Analysis of Stents versus PTA In Renal Arteries) clinical feasibility study. There were no major in-hospital complications reported during the study. There were eight major adverse events in 51 patients out to 720 days, which included four deaths and four cases of target lesion revascularization.

Note: The remaining adverse event information and the information in the subsequent section (Clinical Studies) is based upon the ASPIRE2 Pivotal study.

A total of 208 patients were evaluated as part of the multi-center, prospective, non-randomized study to evaluate the safety and effectiveness of the PALMAZ Balloon-Expandable Stent in patients with atherosclerotic proximal renal artery stenosis that was suboptimally treated with percutaneous transluminal renal angioplasty (PTRA).

As shown in Table 2, there were twenty major device or procedure-related adverse events reported in 208 patients out to 270 days. One patient experienced a significant embolic event postoperatively and died at 80 days of cardiac arrest due to renal failure.

There were eleven deaths (5.2%) that were non-device and procedure related. Five of the deaths were cardiac-related and six were non-cardiac. Two patients died due to myocardial infarction, one patient at 145 days and the other at 253 days. Three patients died due to cardiac arrest: one patient at 90 days, one patient at 127 days and one patient at 243 days. One patient died at 48 days subsequent to an embolic event from the aorta and superior mesenteric artery. One patient died at 81 days following aortic valve replacement surgery. One patient died at 87 days subsequent to viral pneumonia with acute inflammatory pneumonitis and respiratory distress. One patient died at 140 days subsequent to hyperkalemia due to renal failure and severe cardiomyopathy. One patient experienced a device or procedure related significant embolic event at day 7. This patient subsequently died at day 164 due to sepsis. One patient died at day 208 due to a cerebral vascular accident.

Table 2. Device or Procedure Related Observed Adverse Events to 270 Days for the PALMAZ Balloon-Expandable Stent ASPIRE 2 Clinical Study

Parameter	Percent (N=208 Patients)	95% CI
In-hospital Event		
Major Adverse Event (Death, QMI, TLR, Embolic)	3 (1.4%)	[0.3%, 4.2%]

Death (device or procedure-related)	0 (0.0%)	[0.0%, 1.8%]
Q-wave MI	0 (0.0%)	[0.0%, 1.8%]
Target lesion revascularization	0 (0.0%)	[0.0%, 1.8%]
Significant embolic event ⁽¹⁾	3 (1.4%)	[0.3%, 4.2%]
Stent Thrombosis	1 (0.5%)	[0.0%, 2.7%]
CVA	0 (0.0%)	[0.0%, 1.8%]
Major bleeding	2 (1.0%)	[0.1%, 3.4%]
Major Vascular	5 (2.4%)	[0.8%, 5.5%]
Out-of-hospital Event		
Major Adverse Event (Death, QMI, TLR, Emboli)	17 (8.2%)	[4.8%, 12.8%]
Death (device or procedure related)	1 (0.5%)	[0.0%, 2.7%]
Q-wave MI	0 (0.0%)	[0.0%, 1.8%]
Target lesion revascularization	10 (4.8%)	[2.3%, 8.7%]
Significant embolic event ⁽¹⁾	8 (3.8%)	[1.7%, 7.4%]
Stent Thrombosis	1 (0.5%)	[0.0%, 2.7%]
CVA	0 (0.0%)	[0.0%, 1.8%]
Major bleeding	1 (0.5%)	[0.0%, 2.7%]
Major Vascular	5 (2.4%)	[0.8%, 5.5%]
Combined (In-and-Out-of-hospital)		
Major Adverse Event (Death, QMI, TLR, Emboli)	20 (9.6%)	[6.0%, 14.5%]
Death	1 (0.5%)	[0.0%, 2.7%]
Q-wave MI	0 (0.0%)	[0.0%, 1.8%]
Target lesion revascularization	10 (4.8%)	[2.3%, 9.3%]
Significant embolic event ⁽¹⁾	11 (5.3%)	[2.7%, 9.3%]
Stent Thrombosis	2 (1.0%)	[0.1%, 3.4%]
CVA	0 (0.0%)	[0.0%, 1.8%]
Major bleeding	3 (1.4%)	[0.3%, 4.2%]
Major Vascular	10 (4.8%)	[2.3%, 8.7%]

Note: (1) Significant embolic event (SEE) is defined as causing end-organ damage, (e.g., unanticipated kidney/bowel infarct, lower extremity ulceration or gangrene) or loss of kidney function. Five patients were categorized as SEE due to a true embolic event. Three patients were categorized as SEE due to contrast reaction, secondary to acute tubular necrosis (ATN).

6.2 POTENTIAL ADVERSE EVENTS

Adverse events (in alphabetical order) that may be associated with implantation of a stent in renal arteries (in addition to those listed in Table 2) include:

- Allergic reaction to stainless steel or its components
- Aneurysm
- Death
- Dissection
- Embolization of plaque or cholesterol
- Failure to deliver the stent to the intended site
- Fistulization
- Hematoma requiring treatment
- Hemorrhage
- Infection/fever
- Myocardial ischemia/infarction
- Nephrectomy/renal transplantation
- Peripheral neuropathy
- Persistent abdominal pain
- Persistent vessel spasm
- Pseudoaneurysm
- Reaction to contrast media
- Renal failure/dialysis
- Restenosis of vessel (greater than 50% obstruction)
- Rupture or perforation of vessel
- Stent migration or embolization
- Stroke
- Thrombosis/vessel occlusion

6.3 Stent Delivery Failures

Stent treatment of 252 lesions was attempted in the ASPIRE2 Pivotal Study. There were five stent delivery failures. The circumstances of the delivery failures are as follows: stent was deployed distal to the intended location with a second stent successfully delivered (n=3); unable to deploy stent, stent was retrieved and a subsequent stent successfully delivered (n=1); unable to deploy stent, stent was retrieved (n=1).

7.0 CLINICAL STUDY INFORMATION

A feasibility study (ASPIRE) was conducted to evaluate the safety and deliverability of the PALMAZ Balloon-Expandable Stent design in treating proximal renal artery stenosis. A total of 51 patients (N = 63 lesions), at seven investigation centers in the United States, with de novo or restenotic renal artery lesions located in vessels that had a $\geq 70\%$ stenosis, reference vessel diameter of 4 to 7 mm were treated with the PALMAZ Balloon-Expandable Stent. The mean pre-procedure percent diameter stenosis (N = 60 lesions) of 61.3 ± 14.4 , 95% CI of [57.6, 65.1] decreased to 4.6 ± 8.9 , 95% CI of [2.3, 6.9] post-procedure. At one-year follow-up, the percent diameter stenosis (N = 24 lesions) was 26.9 ± 23.8 , 95% CI of [16.8, 36.9]. There were no in-

hospital major adverse events (i.e., death, renal infarct of treated kidney, renal bypass of treated kidney, or revascularization of target lesion). Four deaths and four reports of target lesion revascularization occurred during the two-year follow-up period. The rate of other complications including renal failure, bleeding complications, and vascular complications was 23.5%.

The ASPIRE feasibility study was followed by a multi-center, prospective, non-randomized study (ASPIRE2). The purpose of the ASPIRE2 study was to evaluate the effectiveness and safety of the PALMAZ Balloon-Expandable Stent in patients with atherosclerotic proximal renal artery stenosis that was suboptimally treated with PTRAs, as compared to a pre-specified performance criteria of a 40% nine-month restenosis rate. The study population consisted of 208 patients enrolled at 23 investigational centers in the United States. A total of 252 lesions were treated with one stent placed in 231 lesions and 2 stents placed in 21 lesions. Forty-three patients were treated for bilateral renal artery disease. The ASPIRE2 study is summarized below.

Study Endpoints: The primary endpoint was the restenosis rate at 9-months, determined by duplex ultrasound. Secondary endpoints included:

- Acute procedural success defined as <30% residual stenosis immediately after stent deployment as determined by the Core Laboratory (if no quantitative angiographic analysis was available, visual estimates were used) and ≤ 5 mm Hg residual translesion.
- Worsening renal function defined by a rise in serum creatinine at 30 days, 6 months, 9 months and 24 months:
 - If baseline level is ≤ 2.0 mg/dl, a $\geq 50\%$ increase in serum creatinine.
 - If baseline level is > 2.0 mg/dl, a 1 mg % increase in serum creatinine.
- Blood pressure measurement change / antihypertensive medication at 30 days, 6 months, 9 months and 24 months: cured, improved, no improvement or censored.
- Absence of major adverse events at 30 days, 3 months, 6 months, 9 months and 24 months:
 - Incidence of device or procedure-related death, procedure related Q-wave myocardial infarction, target lesion revascularization (TLR) or significant embolic events (defined as end-organ damage, e.g., unanticipated kidney/bowel infarct, ulcerated or gangrenous foot).

An independent clinical events committee adjudicated all of the major adverse events (MAEs) and other events. Endpoints were analyzed on an intent-to-treat basis

Patients Studied: Eligible patients had either de novo or restenotic renal artery lesions with a $\geq 70\%$ stenosis, a reference vessel diameter of 4 to 8 mm located within 10 mm of the aorta and suboptimally treated with PTR. Patients with a total occlusion of the renal artery or having advanced renal disease as evidenced by serum creatinine of ≥ 3.0 mg/dl or kidney length of < 8 cm were excluded from the study. Baseline characteristics for the patients in the ASPIRE2 study are presented in Table 3.

**Table 3. Baseline Characteristics
(N = 208 patients, 252 lesions)**

Characteristic	
Age (yrs), mean \pm SD (N)	69.6 \pm 9.9 (208)
Number of men	36.5% (76/208)
History of smoking	67.8% (141/208)
History of coronary artery disease	38.5% (80/208)
History of diabetes mellitus	26.0% (54/208)
Atherosclerotic peripheral vascular disease (other than renal artery stenosis)	44.2% (92/208)
Reference vessel diameter (mm), mean \pm SD (N)	4.83 \pm 1.09 (244)
Minimum lumen diameter (mm), mean \pm SD (N)	1.84 \pm 0.75 (244)
Lesion length (mm), mean \pm SD (N)	6.54 \pm 3.23 (242)
Percent diameter stenosis, mean \pm SD (N)	61.5 \pm 13.8 (244)

Methods: Patients eligible for the study underwent a PTR on a single renal artery and had an angiographically documented suboptimal result defined by the presence of unfavorable lesion morphology consisting of one or more of the following: an inadequate angiographic result as defined by a $\geq 50\%$ lumen diameter narrowing; a 20 mm Hg peak translesion pressure gradient; a 10 mm Hg or greater mean translesional pressure gradient; and Grade D dissection or any dissection with significant compromise in lumen flow. Patients were to be treated with no more than two stents per renal artery. Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Clinical follow-up visits were conducted at 30 days, 6 months and 9 months post-procedure. Baseline quantitative angiography was performed pre-procedure, post-PTR, and post-procedure in all patients. Duplex Ultrasound was utilized to make an initial determination of restenosis at the 9-month follow-up. If restenosis was observed by Duplex Ultrasound, a confirmatory angiogram was performed to document the amount of restenosis present. Computer assisted quantitative angiographic analysis (QA) and Duplex Ultrasound were performed at central laboratories.

ASPIRE2 Study Results: In suitable patients, stent placement in renal arteries following failed angioplasty resulted in improved acute angiographic outcomes and a nine month restenosis rate of 17.4%, 95% CI of [11.9%, 21.9%]. Clinical follow-up was available on 93.3% (194/208) and angiographic and/or duplex ultrasound follow-up was available on 73.6% (153/208) of patients at 9 months (270 \pm 30 days). The major adverse event rate (defined as device or procedure related death, Q-wave myocardial infarction, target lesion revascularization, or significant embolic event) at 270 days was 9.6%, 95% CI of [6.0%, 14.5%]. Freedom from target lesion revascularization at 270 days was 95.5% with 95% CI of [93.0%, 98.0%]. The principal effectiveness and safety results are presented in Table 4. The freedom from major adverse events Kaplan-Meier curve is presented in Figure 1.

The ASPIRE2 study included 43 patients who had a contralateral renal artery lesion treated with the PALMAZ Stent. The patients with bilateral stenosis had the most significant lesion treated with PTRAs first. If the results were suboptimal, the lesion was treated with a stent and the patient was enrolled into the study. Treatment of the contralateral lesion involved PTRAs and stent placement, or primary stenting of the lesion. Stent placement in the patients who had both renal arteries treated resulted in a nine month restenosis rate of 16.8%, 95% CI of [7.8%, 26.0%] with a 270-day major adverse event rate of 14.0% with 95% CI of [6.3%, 25.7%]. Freedom from target lesion revascularization at 270 days for the patients treated bilaterally was 97.5% with 95% CI of [94.2%, 100.0%]. The lesion-based endpoint values for patients with bilateral lesions may not be independent, and therefore may be correlated. The effectiveness measures presented herein from the ASPIRE2 study were not based upon the analysis of correlated lesion data, but rather the analysis of independent lesion data. Statistical comparisons between the unilateral and bilateral stented patients revealed no consistent pattern of difference in response to stenting between the two groups.

A twenty-four month follow-up visit was conducted to obtain blood pressure measurements, hematology evaluations and the recording of adverse events. The twenty-four month clinical safety and effectiveness data obtained on the 208 patients enrolled in the ASPIRE2 Study is presented in Table 4. There were a total of 41 major adverse events reported for the 208 patients and consisted of the following: one device or procedure related death, 30 target lesion revascularizations and 10 significant embolic events. Freedom from target lesion revascularization at 720-days was 85.9% with 95% CI of [81.4%, 90.4%]. The mean serum creatinine level at twenty-four months (N = 153 patients) was 1.46 mg/dl \pm 0.81 mg/dl, 95% CI of [1.33, 1.58]. The mean systolic and diastolic blood pressure at twenty-four months (N = 158 patients) was 149.4 mm Hg \pm 25.3 mm Hg, 95% CI of [145.3, 153.2] and 76.9 mm Hg \pm 11.9 mm Hg, 95% CI of [75.0, 78.7], respectively. The mean number of antihypertensive medications reported taken by the patients at twenty-four months (N = 182 patients) was 2.30 \pm 1.26, 95% CI of [2.1, 2.5].

TABLE 4. PRINCIPAL EFFECTIVENESS AND SAFETY RESULTS

Effectiveness Measures	All Patients (N = 208)	95% C.I.
	All Lesions (N = 252)	
Acute Procedure Success	80.2% (182/227)	[74.4%, 85.2%]
Post-Procedure in-lesion % DS	10.26 ± 11.1 (244)	(8.86, 11.67)
Range (min, max)	(-35.3, 61.31)	
Post-Procedure in-stent % DS	-2.17 ± 17.5 (243)	(-4.39, 0.05)
Range (min, max)	(-86.8, 54.24)	
Post-Procedure in-lesion MLD	4.31 ± 0.98 (244)	(4.19, 4.43)
Range (min, max)	(1.62, 6.89)	
Post-Procedure in-stent MLD	4.87 ± 1.07 (243)	(4.74, 5.01)
Range (min, max)	(1.89, 8.50)	
9 Month Restenosis Rate (Lesion based)	17.4% (32/184)	[11.9%, 21.9%]
TLR-free at 270 Days (Lesion Based, K-M)	96.7%	[94.5%, 98.9%]
Primary Patency (QA/Duplex Ultrasound)	81.0% (149/184)	[74.6%, 86.4%]
Primary Patency (Clinical)	96.8% (244/252)	[93.8%, 98.6%]
Secondary Patency (QA/Duplex Ultrasound)	82.6% (152/184)	[76.3%, 87.8%]
Secondary Patency (Clinical)	99.2% (250/252)	[97.2%, 99.9%]
Average Systolic Blood Pressure (mmHg)		
Baseline	167.6 ± 25.2 (208)	[164.2, 171.0]
9 Months*	149.1 ± 24.0 (178)	[145.6, 152.6]
24 Months*	149.3 ± 25.3 (158)	[145.3, 153.2]
Average Diastolic Blood Pressure (mmHg)		
Baseline	81.5 ± 13.1 (208)	[79.8, 83.3]
9 Months*	77.3 ± 12.1 (178)	[75.5, 79.0]
24 Months*	76.9 ± 11.9 (158)	[75.0, 78.7]
Average Number of Antihypertensive Medications		
Baseline	2.8 ± 0.9 (208)	[2.7, 3.0]
9 Months*	2.4 ± 1.2 (196)	[2.2, 2.6]
24 Months*	2.3 ± 1.3 (182)	[2.1, 2.5]
Safety Measures		
In-hospital Major Adverse Events	1.4% (3/208)	[0.3%, 4.2%]
Out-of-hospital Major Adverse Events to 9 Months	8.2% (17/208)	[4.8%, 12.8%]
In-hospital and Out-of-hospital MAEs to 9 Months	9.6% (20/208)	[6.0%, 14.5%]
MAE-free at 270 days (K-M)	90.3%	[88.2%, 94.4%]
In-hospital and Out-of-hospital MAEs to 24 Months	19.7% (41/208)	[14.5%, 25.8%]
Stent Thrombosis (9 Months)	1.0% (2/208)	[0.1%, 3.4%]
CVA (9 Months)	0.0% (0/208)	[0.0%, 1.8%]
Major Bleeding (9 Months)	1.4% (3/208)	[0.3%, 4.2%]
Major Vascular (9 Months)	4.8% (10/208)	[2.3%, 8.7%]
Average Serum Creatinine Level (mg/dl)		
Baseline	1.36 ± 0.52 (207)	[1.29, 1.43]
9 Months	1.40 ± 0.61 (173)	[1.30, 1.49]
24 Months	1.46 ± 0.81 (153)	[1.33, 1.58]

Numbers are % (count/available field sample size) Mean ± Standard Deviation or Range (Min,Max).

CI – Confidence Interval

*P-value of <.001 for the test for difference of means between each time point and baseline, based on paired t-test.

Acute Procedure Success - Acute procedure success was defined as angiographic success of < 30% residual stenosis as determined by the Core Laboratory (if no QA, visual estimates were used), and ≤ 5 mmHg mean residual gradient.

Restenosis - \geq 50% diameter stenosis by QA at 9 month follow-up or if QA not available then renal to aortic ratio within the stent of 3.5 or greater or an absolute peak systolic velocity within the stent greater than 200 cm/sec via duplex ultrasound.

TLR-free at 270 Days - No target lesion revascularization within 270 Days using Kaplan-Meier estimates.

Primary Patency (Angiographic or Duplex Ultrasound) - $<$ 50% diameter stenosis by QA at 9 month follow-up or if QA not available then a renal to aortic ratio within the stent of less than 3.5 and an absolute peak systolic velocity within the stent less than 200 cm/sec via duplex ultrasound performed 9 months post-study procedure without any reintervention.

Secondary Patency (Angiographic or Duplex Ultrasound) - $<$ 50% diameter stenosis by QA at 9 month follow-up or if QA not available then a renal to aortic ratio within the stent of less than 3.5 and an absolute peak systolic velocity within the stent less than 200 cm/sec via duplex ultrasound performed 9 months post-study procedure with or without repeat percutaneous reintervention.

Primary Patency (Clinical) - No target lesion revascularization through last follow-up.

Secondary Patency (Clinical) - No repeated target lesion revascularization through last follow-up.

Major Adverse Event (MAE)** - The following procedure or device related events were considered to be major adverse events:

-death

-Q-wave myocardial infarction

-target lesion revascularization

-loss of kidney function or significant embolic events

** - Major Adverse Events were adjudicated by the Clinical Events Committee

Stent Thrombosis - After successful stent deployment, angiographic thrombus within the stented vessel during the first 30 days following stent deployment.

CVA - Acute neurological deficits recorded by the clinical sites.

Major Bleeding - Transfusion of blood products due to blood loss resulting from the percutaneous revascularization procedure, or blood loss resulting in change in anticoagulation regimen.

Major Vascular - Occurrence of hematoma, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure related transfusion, or vascular surgical repair.