# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## 1. General Information

Device Generic Name: Renal Stent

Device Trade Name: PALMAZ® Balloon Expandable Stent for the Renal Arteries

Applicant's Name and Address: Cordis Corporation
P.O. Box 4917
Warren, NJ 07059

Premarket Approval Application (PMA) Number: P890017/S10

Date(s) of Panel Recommendation: None

Date of Notice of Approval to Applicant: July 10, 2002

The PALMAZ® Balloon Expandable Stent, Model P308, was approved on September 29, 19991 (P890017) for use following a suboptimal angioplasty procedure of the common or external iliac arteries. The sponsor submitted this supplement for the PALMAZ® Balloon Expandable Stent, Models P104R, P154R and P204R, to expand the indication for use in the renal arteries. The updated pre-clinical and clinical data to support this indication are provided in this summary. Some of the pre-clinical tests were presented in the original PMA application. For more information on the data that supported approval of the indication or use in the iliac arteries, the summary of safety and effectiveness data (SSED) for P890017 should be referenced. Written requests for copies of the SSED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. The SSED can also be found on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html.

## 2. Indications 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) ≥50% residual stenosis by visual estimate
2) ≥20mmHg peak translesional pressure gradient
3) ≥10mmHg 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. 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.

**Table 1. Device Models**

| Stent Description | | Stent Lengths | | | Recommended Cordis Catheter Sheath Introducer (CSI) and Guiding Catheter | |
|---|---|---|---|---|---|---|
| Product Code | Nominal Dia (mm) | Unexpanded (mm) | Expanded (mm) | Catalog Number[1] | 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.

## 4. 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.

## 5. WARNINGS and PRECAUTIONS

See WARNINGS and PRECAUTIONS in the final labeling (Instructions for Use).

# 6. 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%] |

| Parameter | Percent (N=208 Patients) | 95% CI |
|---|---|---|
| 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. Alternative Procedures

Alternative procedures to treat renal artery stenosis include percutaneous transluminal renal angioplasty (PTRA) and surgical procedures (e.g., aorto-renal bypass, extra-anatomic bypass, combined aortic graft and aorto-renal bypass, adjunctive transaortic renal endarterectomy).

## 8. Marketing History

The PALMAZ Balloon-Expandable Medium Stents were first sold commercially in 1991 by Johnson & Johnson Interventional System Company. Since that time, more than 225,000 of these devices have been distributed throughout the world, including the European Union, Eastern Europe, Canada, Latin America, and Australia. The device has been available in the United States since 2000 for use in the treatment of atherosclerotic lesions of the common or external iliac artery following suboptimal angioplasty procedure and since 1991 for the palliation of malignant neoplasms in the biliary tree.

The device has not been withdrawn from marketing in any of these countries for any reason related to safety and effectiveness.

## 9. Summary of Pre-clinical Studies

### 9.1 Biocompatibility

The material and manufacturing methods used to construct the PALMAZ Balloon-Expandable Medium Stents (Models P104R, P154R and P204R) are identical to the materials and manufacturing methods used to construct the approved PALMAZ Balloon-Expandable Stents Model P308 approved under P890017. Therefore the biocompatibility testing provided in the original premarket approval application P890017 is also applicable to the current application for the PALMAZ Balloon-Expandable Medium Stents.

Biocompatibility of the materials used in the construction of the POWERFLEX Plus delivery catheter was determined by the results of previous testing conducted on these materials or combination of materials, as well as testing conducted on the finished POWERFLEX Plus catheter. The testing, including those recommended in the FDA modified matrix of International Standard ISO-10093, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing," were: cytotoxicity, sensitization, irritation, systemic toxicity, implantation, hemolysis, hemocompatibility, pyrogenicity, and physio-chemical testing. The results of all biocompatibility tests were acceptable.

## 9.2 Bench Testing

**Previous Preclinical Studies**

The PALMAZ Balloon-Expandable Stent Model P308 was commercially approved for marketing under the original premarket approval application P890017. The PALMAZ Balloon-Expandable Medium Stent Models P104R, P154R and P204R differ from the PALMAZ Balloon-Expandable Stent Model P308 only in length and the specified expansion diameter. Therefore, the preclinical testing of the stent wire material (material specification, mechanical properties and corrosion resistance), and compatibility with magnetic resonance imaging provided in P890017 is applicable to the PALMAZ Stent Models P104R, P154R and P204R. Please refer to the SSED of the original PMA P890017 for a summary of this testing.

**Additional Pre-Clinical Studies**

The PALMAZ Balloon-Expandable Stent Models P104R, P154R and P204R have undergone additional pre-clinical testing as follows:

**Stent Testing**

*Stent Free Area and Dimensional Change*
The stent free area, i.e., the open area of the stent and the change in stent length was calculated for all diameters that the Palmaz stent could theoretically be expanded to. The percent free area for all stent lengths ranged from 80.65% for the smallest diameter (4 mm) to 88.87% for the largest diameter (8 mm). The calculated stent length decreased a maximum of 15% for the 10 mm nominal length and 16% for the 15 mm and 20 mm nominal stent lengths with the stent expanded to largest diameter (8 mm). The percentage of free area with the PALMAZ Stent is similar to the percentage of free area with stents approved for the vascular system.

*Stent Recoil*
Stent recoil is calculated as a function of the pressurized stent diameter while on the balloon, and the stent diameter after the balloon is deflated and removed. The acceptance criterion is < 10% recoil for any length - diameter combination. The worst case situation is the smallest expansion diameter (4mm) since the stent would need to recoil the smallest absolute distance to reach the 10% threshold. In addition to the 4mm diameter, 5 and 8mm diameters were also tested. Five (5) stents of each length were tested. All stents satisfactorily met the recoil criteria.

*Stent Uniformity*
Stent Uniformity data is captured as part of Stent Recoil testing. Since all stents were within 10% of their stated diameter, they have also opened uniformly. Stent Uniformity data is based on the relaxed stent diameters.

*Radial Strength*
To determine the radial strength of the stent, five samples of each stent length were expanded to the maximum diameter (8mm) within a latex tube. The latex tube with expanded stent was placed in a pressure vessel and circumferential pressure was applied until the stent collapsed (irreversible stent deformation). All stents exceeded the acceptance criteria with the average radial pressure to collapse of the stent 5.3 psi for the 10 mm length, 4.4 psi for the 15 mm length and 7.8 psi for the 20 mm length.

*Stress and Fatigue Testing*
Stress and Fatigue Testing was conducted on P394 Palmaz Stents, which are identical in design to the Palmaz Stent models P104R, P154R with the exception of a longer stent length. A total of 10 stents expanded to 9 mm (1 mm greater than the maximum labeled diameter) were subjected to fatigue testing with a pulsed pressure of 100 mm Hg pressure for a maximum of 614 million cycles. The stents were examined under scanning electron microscopy (SEM) after 100, 400, 500 and 614 million cycles. The SEM examination did not show any metallurgical defects that could cause failure of the stent.

To further assess the fatigue strength of the Palmaz Stent in the renal artery, a finite elements analysis (FEA) was conducted on the 20 mm long (P204) Palmaz Stent expanded to 9 mm and a 300 mm Hg pressure differential. The results of the FEA indicated a satisfactory safety factor was present and fatigue failure of the stent was unlikely.

**Stent and Delivery System Testing**

*Maximum Balloon Pressure*
To determine the burst strength of the PowerFlex Plus delivery catheter with the mounted Palmaz Stent, a total of 50 samples (10 each of the extreme balloon diameters and lengths and a medium-sized stent diameter) were tested to burst. The test results showed with a 95% confidence that 99.9% of the stented balloons would not burst at or below the labeled rated burst pressure of 15 atm.

*Stent Diameter versus Balloon Inflation Pressure*
To assess the change in stent diameter with inflation of the delivery catheter balloon, 45 stent/catheter systems representing each balloon length and diameter were inflated in 1 atmosphere increments up to the rated burst pressure. The test results showed that all of the stent diameters were within 10% of the labeled stent diameter when expanded with inflation pressures from the nominal 10 atm up to the rated burst pressure of 15 atm.

*Balloon Deflatibility and Deflation Time*
To evaluate the ability to deflate and withdraw the balloon and determine the time to deflate 90% of the balloon, 19 stent/catheter systems representing the smallest and largest balloon diameter and length and the longest catheter shaft length were tested. All the test samples met the acceptance criteria for the smallest and largest balloon diameter, $\leq$ 9.5 seconds and $\leq$ 21 seconds, respectively.

*Bond Strength*
To determine the strength of the bonds used in the construction of the delivery catheter, tensile testing was conducted on five samples each of the following bonds: proximal and distal balloon to catheter bond, marker band to inner catheter, and y-connector to catheter bond. The test results found that the strength of the bonds exceeded the acceptance criteria of $\geq$ 8 Newtons for the balloon to catheter and marker band to inner catheter bonds. The tensile test results of the y-connector to catheter bond also exceeded the acceptance criterion of $\geq$ 15 Newtons.

*Stent Crimping (Stent Retention)*
To determine the minimum tensile force required to dislodge the Palmaz Stent from the delivery catheter balloon, ten samples of the shortest stent/balloon combination (4mm stent diameter by 10mm long balloon) were tensile tested. All of the stent/balloon catheter samples met the acceptance criteria of $\geq$ 0.7 Newtons.

*Crossing Profile*
To determine the crossing profile of the stent/catheter system, the outer diameter measurement were taken of 45 Palmaz Stent samples mounted on 45 delivery catheters representing each balloon length and diameter were measured. The crossing profile measurements found that the 4 mm, 5mm and 6 mm diameter stent/catheter systems are compatible with 6 Fr.catheter sheath introducers and the 7 mm and 8 mm diameter stent/catheter systems are compatible with 7 Fr.catheter sheath introducers.

*Catheter Body Maximum Pressure*
To determine the maximum pressure limits of the delivery catheter's balloon inflation lumen and guidewire lumen, 10 samples were tested to failure. The test results found that both lumens exceeded their respective acceptance criteria; $\geq$ 15 atm for the balloon inflation lumen and $\geq$ 33 atm for the guidewire lumen.

*Contrast Medium Flow*
To evaluate the use of the catheter for injection of contrast medium at pressures ranging from 10 atm to 30 atm, 5 samples of the shortest catheter length (40 cm) and 5 samples of a worst case longest catheter length (150 cm) were tested. The test results showed that the average flow rate per minute for the 40 cm length ranged from 4.9 cc with 10 atm to 13.2 cc with 30 atm. The average flow rate per minute for the 150 cm length ranged from 1.7 cc with 10 atm to 5.1 cc with 30 atm. All test samples met the acceptance criteria of no leaking, bulging or burst catheter failures.

## 9.3 Sterility Packaging and Shelf Life Testing

*Sterility*
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 Stents Model P308 approved under P890017. Therefore the sterility testing provided in the original premarket approval application P890017 is also applicable to the current application for the PALMAZ Balloon-Expandable Medium Stents.

The POWERFLEX Plus delivery catheter is sterilized using an ethylene oxide sterilization process. Validation of the sterilization process for the POWERFLEX Plus delivery catheter is based on the ANSI/AAMI/ISO 1135-1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization." The validation results demonstrated that the sterilization process can achieve a sterility assurance level of $10^{-6.}$

*Packaging and Shelf-life Tests*
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 ≥ 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 PTRA, 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 PTRA. 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 ± SD(N) | 4.83 ± 1.09 (244) |
| Minimum lumen diameter (mm), mean± SD(N) | 1.84 ± 0.75 (244) |
| Lesion length (mm), mean ± SD (N) | 6.54 ± 3.23 (242) |
| Percent diameter stenosis, mean ± SD (N) | 61.5 ± 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 =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 ±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 ± 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 ± 25.3 mm Hg, 95% CI of [145.3, 153.2] and 76.9 mm Hg ± 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 ± 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**

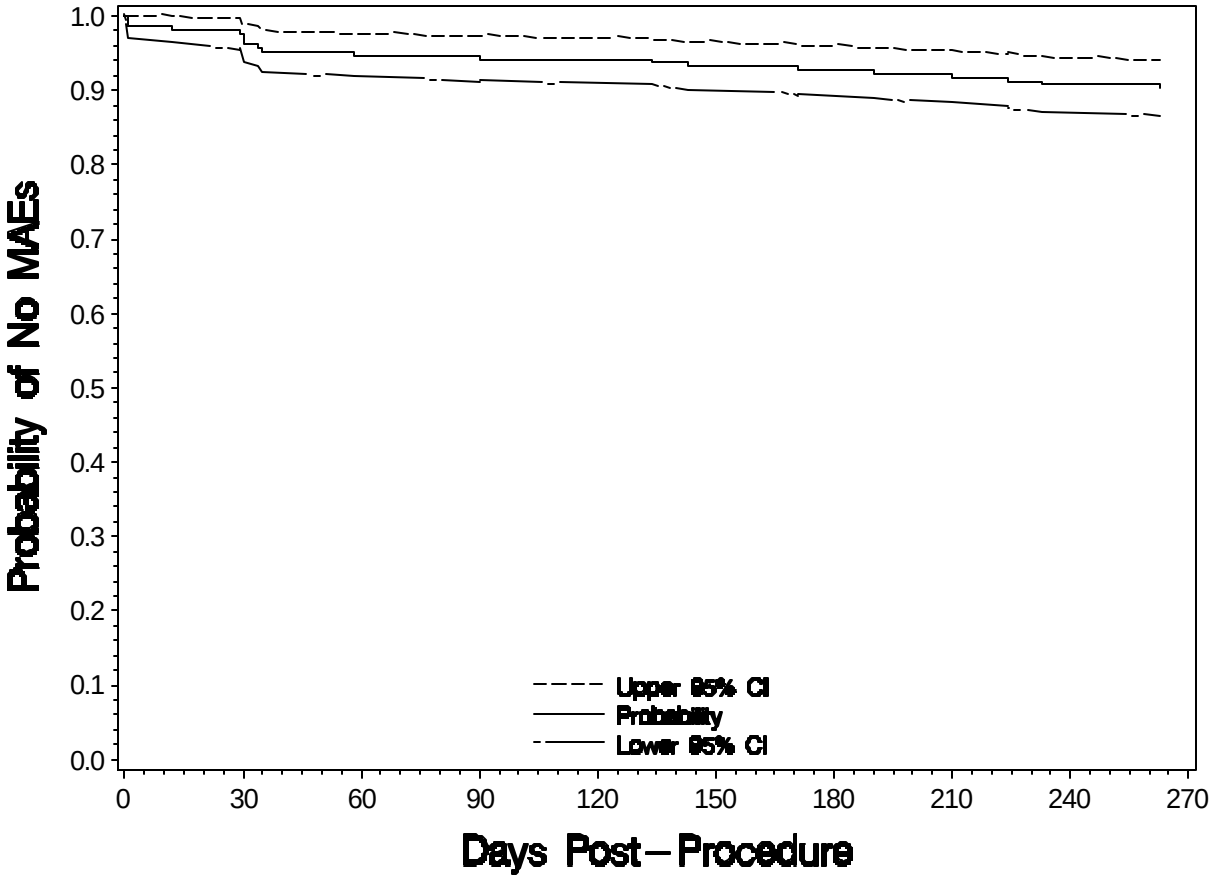
| Effectiveness Measures – Lesions | All Lesions (N=252) | 95% C.I. |
|---|---|---|
| Acute Procedure Success | 80.2% (182/227) | [74.4%, 85.2%] |
| Post-Procedure in-lesion % DS | 10.26 ± 11.1 (244) | (8.86, 11.67) |
| Range (min, max) | (-35.3, 61.31) | |
| Post-Procedure in-stent % DS | -2.17 ± 17.5 (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.