SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System
Device Trade Name:	PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ and Over-The-Wire)
Name and Address of Sponsor:	Boston Scientific Corporation One Scimed Place Maple Grove, MN 55311
Premarket Approval Application (PMA) Number:	P110010
Date of Panel Recommendation:	None
Date of FDA Notice of Approval:	November 22, 2011
Expedited:	Not Applicable

II. INDICATIONS FOR USE

The PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients with symptomatic heart disease due to *de novo* lesions in native coronary arteries ≥2.25 mm to ≤4.00 mm in diameter in lesions ≤28 mm in length.

III. CONTRAINDICATIONS

Use of the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is contraindicated in patients with known hypersensitivity to:

- 316L stainless steel or platinum
- everolimus or structurally-related compounds
- the polymers or their individual components (see details in Section V – DEVICE DESCRIPTION)

Coronary Artery Stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System Directions for Use (DFU).

V. DEVICE DESCRIPTION

The PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is a device/drug combination product comprised of two regulated components:

- A device (Element Coronary Stent System)
- A drug (a formulation of everolimus contained in a polymer coating).

The characteristics of the PROMUS Element Plus Stent System are described in **Table 1**.

Table 1: PROMUS Element Plus Stent System Product Description

	PROMUS Element Plus Monorail Stent Delivery System	PROMUS Element Plus Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32*	
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.0032 inches (0.081 mm) for diameters 2.25 mm to 3.50 mm 0.0034 inches (0.086 mm) for diameter 4.00 mm	
Drug Product	A conformal coating of a polymer carrier loaded with 100 µg/cm² everolimus applied to the stent with a maximum nominal drug content of 177.3 µg on the largest stent (4.00 x 28 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 26 cm from tip. Designed for guidewire ≤0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa)	
	Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	
Catheter Shaft Outer Diameter	2.3 F (≤0.80 mm) proximal and 2.7 F (≤0.95 mm) distal.	3.4F (≤1.20 mm) proximal for 2.25 to 4.00 mm sizes 2.4F (≤0.85 mm) distal for 2.25 to 2.75 mm sizes 2.7F (≤0.95 mm) distal for 3.00 to 4.00 mm sizes
Guide Catheter Minimum Inner Diameter Requirement	≥0.056 inches (1.42 mm)	≥0.066 inches (1.68 mm)

* 32 mm length is only available in the 2.25 mm diameter

A. Device Component Description

The PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is a device/drug combination product consisting of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The drug/polymer coating consists of a polymer, PVDF-HFP, and the active pharmaceutical ingredient, everolimus.

Each stent is coated with 100 µg/cm^2 of everolimus of per mm^2 stent surface area in a formulation of 1:4.9 (w/w) drug-to-polymer ratio. This is the same dose density and formulation

used on the commercially available The XIENCE V® and XIENCE nano Everolimus Eluting Coronary Stent System (P070015) and XIENCE PRIME Everolimus Eluting Coronary Stent System (P110019). The PtCr alloy used for the PROMUS Element Stent provides increased strength and radiopacity compared to the 316L stainless steel used in several first-generation stents from BSC such as TAXUS Express[2] and TAXUS Liberté stents (P030025 and P060008, respectively). The same PtCr Element stent platform is used in the ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System (P100023).

The PROMUS Element Stent is the everolimus-coated member of the platinum chromium (PtCr) Element Stent Series. The Element stent is available in four stent models each engineered for specific diameters to provide consistent stent-to-artery ratios across the range of reference vessel diameters indicated:

- Small Vessel (SV): 2.25 mm
- Small Workhorse (SWH): 2.50 mm and 2.75 mm
- Workhorse (WH): 3.00 mm and 3.50 mm
- Large Vessel (LV): 4.00 mm

The commercial matrix is shown in **Table 2** below:

Table 2: PROMUS Element Plus Stent System Commercial Size Matrix

Stent Model	Diameter (mm)	Stent Length in mm						
		8	12	16	20	24	28	32
SV	2.25 mm	X	X	X	X	X	X	X
SWH	2.50 mm	X	X	X	X	X	X	NA
	2.75 mm	X	X	X	X	X	X	NA
WH	3.00 mm	X	X	X	X	X	X	NA
	3.50 mm	X	X	X	X	X	X	NA
LV	4.00 mm	X	X	X	X	X	X	NA

B. Drug Component Description

The PROMUS Element Stent coating consists of two layers, a primer layer and a drug matrix layer. The primer layer is composed of poly (n-butyl methacrylate) (PBMA). The drug matrix layer contains poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) blended with the anti-proliferative drug everolimus.

B1. Everolimus

The active pharmaceutical ingredient in the PROMUS Element Stent is everolimus. The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin, and its chemical structure is provided in **Figure 1**. The nominal total loaded dose of everolimus per nominal stent length/diameter is shown in **Table 3**.

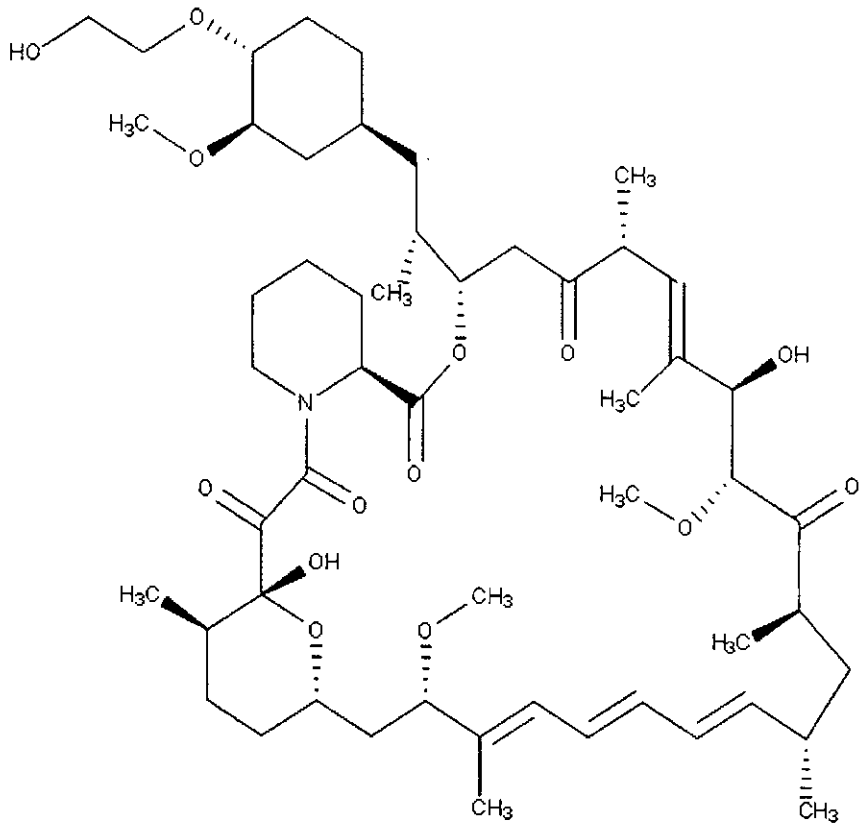

Figure 1: Structure of Everolimus

Table 3: Nominal Total Loaded Dose of Everolimus (µg) per Nominal Stent Length and Diameter

Stent Model		Stent Length						
Design	**Diameter**	**8 mm**	**12 mm**	**16 mm**	**20 mm**	**24 mm**	**28 mm**	**32 mm**
Total Loaded Dose Everolimus/ Stent (µg)	**SV**	38.2	57.3	72.7	91.8	107.2	126.3	145.5
	SWH	38.9	60.6	78.0	95.4	112.7	130.1	N/A
	WH	42.0	60.1	84.3	102.4	120.5	138.6	N/A
	LV	56.1	80.4	104.6	128.8	153.0	177.3	N/A

SV – Small Vessel (2.25 mm)
SWH – Small Workhorse (2.50 mm and 2.75 mm)
WH – Workhorse (3.00 mm and 3.50 mm)
LV – Large Vessel (4.00 mm)
N/A – size not available

B2. Inactive Ingredients

Primer Polymer and Drug Matrix Copolymer Carrier

The PROMUS Element Stent contains a primer polymer layer, PBMA, poly (n-butyl methacrylate), that functions as an adhesion promoter between the bare metal and the drug matrix layer. The chemical structure of PBMA is shown in **Figure 2**.

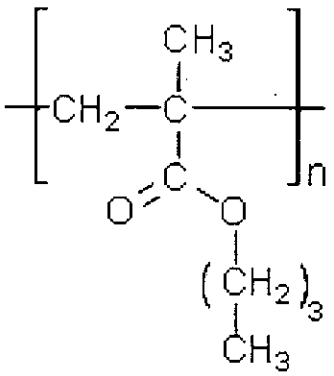

Figure 2: Formula for Poly (n-butyl methacrylate) Polymer (PBMA)

The drug matrix layer contains a semi-crystalline random copolymer, PVDF-HFP, poly (vinylidene fluoride-co-hexafluoropropylene), blended with everolimus. The chemical structure of PVDF-HFP is shown in **Figure 3**.

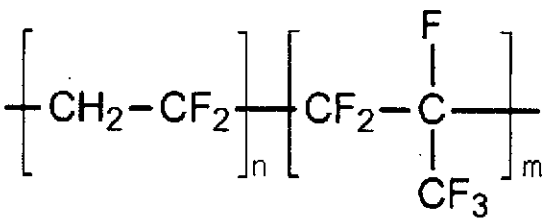

Figure 3: Formula for Vinylidene Fluoride and Hexafluoropropylene Copolymer (PVDF-HFP)

C. Mechanism of Action

The mechanism by which the PROMUS Element Stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Treatment of patients with coronary artery disease may include exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass graft surgery (CABG). 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. MARKET HISTORY

As of December 31, 2010, the PROMUS Element Everolimus-Eluting Coronary Stent System was commercially available in the following countries:

Albania	Algeria	Andorra	Antigua/Barbuda
Argentina	Armenia	Aruba	Australia
Austria	Azerbaijan	Bahamas	Bahrain
Bangladesh	Barbados	Belgium	Belize
Belarus	Bermuda	Bolivia	Bosnia
Brazil	Brunei	Bulgaria	Chile
Colombia	Costa Rica	Croatia	Cyprus
Czech Republic	Denmark	Djibouti	Dominican Republic
Dutch Antilles	Ecuador	Egypt	El Salvador
Estonia	Finland	France	Georgia
Germany	Great Britain	Greece	Guatemala
Guyana	Haiti	Honduras	Hong Kong
Hungary	Iceland	India	Ireland
Indonesia	Israel	Iraq	Italy
Jamaica	Jordan	Kenya	Korea
Kuwait	Latvia	Lebanon	Libya
Liechtenstein	Lithuania	Luxembourg	Macedonia
Macau	Malaysia	Malta	Martinique
Moldavia	Morocco	Myanmar	Nepal
Netherlands	New Zealand	Nicaragua	Norway
Oman	Pakistan	Palestinian Territory	Panama
Paraguay	Peru	Philippines	Poland
Puerto Rico	Portugal	Qatar	Romania
Russia	Saudi Arabia	Serbia	Singapore
Slovakia	Sir Lanka	Slovenia	South Africa
Spain	Surinam	Sweden	Switzerland
Syria	Taiwan	Thailand	Trinidad/Tobago
Tunisia	Turkey	Ukraine	United Arab Emirates
Venezuela	Vietnam	Yemen	

As of October 31, 2011, approximately 577,532 stents have been distributed outside the United States (OUS). No products have been withdrawn from the market in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Bleeding
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, which may require transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal insufficiency or failure
- Respiratory failure
- Restenosis of stented segment
- Stent embolization or migration
- Stent fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day.

Outside the U.S., Zortress® is sold under the brand name, Certican®, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor ®for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses listed above . The amount of drug that circulates in the bloodstream following implantation of a PROMUS Element stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day, see Section 7.2, Pharmacokinetics).

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CY3PA4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)

- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, back, chest, musculoskeletal
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

Please refer to the observed events from the PLATINUM clinical study, which are presented in **Section X – Summary of Primary Clinical Studies**.

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies were performed to evaluate:

- The stent and the stent delivery system [i.e., the stent on either the Monorail (MR) or Over-The-Wire (OTW) stent delivery system (SDS)]
- The polymer substance (i.e., PBMA and PVDF-HFP)
- The drug substance (i.e., everolimus)
- The finished combination product

These evaluations included biocompatibility studies, in vivo pharmacokinetics, in vitro engineering studies, coating characterization, chemistry manufacturing and controls testing, stability, sterilization, and animal studies.

A. Biocompatibility Studies

A series of Good Laboratory Practice (GLP) biocompatibility tests were conducted to demonstrate that the components of the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) are biocompatible. Testing was conducted separately for the stent implant and the stent delivery system. Tests were conducted on ethylene oxide-sterilized bare metal, platinum chromium alloy (PtCr) stents, drug

and polymer coated stents, and stent delivery systems. These test articles were processed in a manner similar to the finished PROMUS Element Plus product. There were some manufacturing differences that were determined not to impact the biocompatibility of the final device, as the surface treatment, coating processing, amount of drug/polymer coating, and sterilization processes were equivalent for both the finished PROMUS Element Stents and test articles utilized during testing.

All biocompatibility testing was conducted in accordance with:

- Guidance for Industry and FDA Staff: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010
- ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing (2003)
- Good Laboratory Practices Regulations (§21CFR 58)

The biocompatibility studies are summarized in **Table 4**.

Table 4.1: Biocompatibility Test Summary (Stent)

Test / Applicable ISO 10993 Part No.	**Test Article**	**Test Result**
Cytotoxicity (L929 MEM Elution) / Part 5	PROMUS Element Stent	Pass
Cytotoxicity (Direct Contact) / Part 5	PROMUS Element Stent	Pass
Sensitization (Guinea Pig Maximization) / Part 10	PROMUS Element Stent	Pass
Intracutaneous Reactivity / Part 10	PROMUS Element Stent	Pass
Acute Systemic Toxicity / Part 11	PROMUS Element Stent	Pass
Material-Mediated Pyrogenicity (Rabbit) / Part 11	PROMUS Element Stent	Pass
13-week Systemic Toxicity following Subcutaneous Implantation in Rats / Parts 6 and 11	PROMUS Element Stent Control: Uncoated PROMUS/Xience V Stent	Pass
Ames Mutagenicity / Part 3	PROMUS Element Stent	Pass
In vitro Mouse Lymphoma / Part 3	PROMUS Element Stent	Pass
In vivo Mouse Micronucleus / Part 3	PROMUS Element Stent	Pass
Hemolysis (Direct Contact) / Part 4	PROMUS Element Stent	Pass
Hemolysis (Extract Method) / Part 4	PROMUS Element Stent	Pass
Complement Activation (C3a and SC5b-9)/ Part 4	PROMUS Element Stent	Pass
Supportive Analytical Chemistry Tests		
Chemical Characterization (Extractables - ICP Analysis)	Uncoated Element Stent	Pass
Chemical Characterization (Residuals and Leachables)	Uncoated Element Stent	Pass

Sub-chronic toxicity, in vivo thrombogenicity, and implantation of the final PROMUS Element stent, containing all components and processing were evaluated in a porcine model of stent-mediated vascular injury. See a summary of this study in Section G - Animal Studies, below.

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Carcinogenicity and Reproductive toxicity testing on the PROMUS Element Stent was not conducted because:

- The chemical composition of the Platinum Chromium Alloy is known and material characterization testing conducted for the bare Element Stent demonstrated that the types and quantities of residues or leachables present from the finished stent do not raise concerns for carcinogenicity.
- Everolimus has been extensively studied. The concentration of Everolimus (100µg/cm2) used in this application and the amounts used are equivalent to the concentrations used in the approved PROMUS® / Xience® V stents (P070015); therefore carcinogenicity and reproductive toxicity testing that was previously conducted on the Xience V product is applicable to the PROMUS Element Plus product. For more details, please refer to the SSED for PROMUS® / Xience® V stents located: http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf
- The PVDF and PBMA polymer coating processes and amounts are equivalent to that used in the approved PROMUS® / Xience® V stents (P070015); therefore carcinogenicity and reproductive toxicity testing that was previously conducted on the Xience V product is applicable to the PROMUS Element Plus product. For more details, please refer to the SSED for PROMUS® / Xience® V stents located: http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf

Table 4.2: Biocompatibility Test Summary (Delivery Systems)

Test / Applicable ISO 10993 Part No.	Test Article	Test Result
Cytotoxicity (L929 MEM Elution) / Part 5	PROMUS Element Plus MR and OTW SDS PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass
Cytotoxicity (Direct Contact) / Part 5	PROMUS Element Plus MR and OTW SDS PROMUS Element MR SDS ION OTW SDS	Pass
Sensitization (Guinea Pig Maximization) / Part 10	PROMUS Element Plus MR SDS PROMUS Element MR SDS ION OTW SDS+ SIBS coated Element Stent	Pass

Test / Applicable ISO 10993 Part No.	Test Article	Test Result
Intracutaneous Reactivity / Part 10	PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass
Acute Systemic Injection / Part 11	PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass
Material-Mediated Pyrogenicity (Rabbit) / Part 11	PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass
Hemolysis (Direct Contact) / Part 4	PROMUS Element Plus MR and OTW SDS PROMUS Element MR SDS ION OTW SDS+ SIBS coated Element Stent	Pass
Hemolysis (Extract) / Part 4	PROMUS Element Plus MR and OTW SDS PROMUS Element MR SDS ION OTW SDS	Pass
		Pass
Complement Activation (C3a and SC5b-9) / Part 4	PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass
Supportive Analytical Chemistry Tests		
USP Physicochemical Test for Plastics / Part 18	PROMUS Element Plus MR and OTW SDS PROMUS Element MR SDS ION OTW SDS + SIBS coated Element Stent	Pass

The commercial PROMUS Element Plus Monorail (MR) and Over-the-Wire (OTW) delivery systems are slightly different from those used in the PROMUS Element MR biocompatibility testing and the PLATINUM clinical trials. The commercial delivery systems consist of the identical materials and similar design and processing to that of PROMUS Element MR biocompatibility test samples and the ION Paclitaxel-Eluting Platinum Chromium Coronary Stent MR and OTW Systems (P100023). The data provided support that any differences between the commercial PROMUS Element Plus delivery systems and the PROMUS Element MR biocompatibility test samples and the

approved ION MR and OTW delivery systems will not affect the biocompatibility of the final product. Therefore the data from the PROMUS Element MR biocompatibility testing and the ION stent MR and OTW delivery system testing are applicable to the PROMUS Element stent MR and OTW delivery systems.

The applicant did not conduct traditional in vivo thrombogenicity on the PROMUS Element MR and OTW delivery systems. The potential for thrombogenicity was evaluated in a porcine model of stent mediated vascular injury. See a summary of this study in Section G – Animal studies, below. Use of the vascular implant study in the porcine model was deemed acceptable because the materials of manufacture, design, and processing methods for the delivery system are equivalent to the approved Apex balloon catheter (P860019/S028) and ION stent delivery system.

Based on the testing performed for the Element stent and delivery systems, as well as the established biocompatibility and safety data on everolimus, PBMA and PVDF-HFP, it can be concluded that the PROMUS Element Plus Everolimus–Eluting Platinum Chromium Coronary Stent System is biocompatible for its intended use.

B. In Vivo Pharmacokinetics

B1. PROMUS Element Plus Everolimus–Eluting Platinum Chromium Coronary Stent

Boston Scientific has provided a letter from the drug substance manufacturer authorizing access to the drug substance section of their everolimus New Drug Applications (NDAs) in support of this application. The drug substance manufacturer produces tablet forms of everolimus, Certican and Zortress, approved for organ transplant rejection prophylaxis indications and Afinitor for renal carcinoma treatment indications. In vivo animal and in vitro pharmacology and toxicology studies, as well as in vivo animal and human pharmacokinetic studies, were conducted on everolimus to provide information about systemic, regional and local toxicity, dose-related toxicity, distribution profiles, end-organ disposition, drug metabolism, and potential drug-drug interactions.

Given that the polymer coating and drug matrix layer components of PROMUS Element Plus are identical to that of the PROMUS® (Xience® V) Everolimus Eluting Coronary Stent System (P070015), the evaluation of PROMUS® (Xience® V) is also applicable to PROMUS Element Plus.

The pharmacokinetics (PK) of everolimus eluted from the PROMUS Element stent post-implantation have been evaluated in patients from two different geographies (the United States of America [USA] and Japan) in a non-randomized sub-study of the PLATINUM clinical trial. The design of the sub-study is described in **Section X - Summary of Primary Clinical Studies**. Whole blood everolimus PK parameters are provided in **Table 5** for groups with 3 or more patients receiving the PROMUS Element Stent.

Table 5: Whole Blood Everolimus Pharmacokinetic Parameters (Mean ± SD) for PLATINUM Groups with Three or More Patients Following PROMUS Element Stent Implantation

Region	USA	Japan		Combined		
Dose (μg)	102.4 μg	102.4 μg	138.6 μg	95.4 μg	102.4 μg	138.6 μg
n	3	4 [b]	3 [b]	4 [c]	7 [b]	3 [b]
t_{max}: (h)	0.66 ± 0.27	0.60 ± 0.22	0.52 ± 0.09	0.47 ± 0.03	0.62 ± 0.23	0.52 ± 0.09
C_{max}: (ng/mL)	0.58 ± 0.078	0.73 ± 0.17	0.91 ± 0.20	0.71 ± 0.09	0.67 ± 0.15	0.91 ± 0.20
AUC_{0-t}: (ng.h/mL)	4.77 ± 1.70	7.71 ± 6.97	10.87 ± 7.36	7.27 ± 4.97	6.45 ± 5.26	10.87 ± 7.36
AUC_{0-24h}: (ng.h/mL)	5.76 ± 0.85	6.42 ± 1.30	9.51 ± 0.64	6.83 ± 2.03	6.14 ± 1.10	9.51 ± 0.64
$AUC_{0-\infty}$: [a] (ng.h/mL)	NA	11.91 ± 1.39	60.74 ± 25.95	19.26 ± 11.69	12.95 ± 2.05	60.74 ± 25.95
$t_{1/2}$: [a] (h)	NA	18.77 ± 2.11	136.06 ± 62.08	34.19 ± 20.81	22.83 ± 7.20	136.06 ± 62.08
CL: [a] (L/h)	NA	8656 ± 1005	2511 ± 1073	6445 ± 3924	8044 ± 1276	2511 ± 1073

NA: Not assessable
a: Accurate determination not possible
b: n=2 for $AUC_{0-\infty}$, $t_{1/2term}$ and CL
c: n=3 for $AUC_{0-\infty}$, $t_{1/2term}$ and CL
t_{max} (h)= time to maximum concentration.
C_{max}= maximum observed blood concentration.
$t_{1/2}$ (h)= terminal phase half-life.
AUC_{0-t}= the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
AUC_{0-24h} = the area beneath the blood concentration versus time curve: time zero to 24 hours post-implant
$AUC_{0-\infty}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance

The results show that individual whole blood concentrations of everolimus tended to increase in proportion to the total dose. Individual t_{max} values ranged from 0.42 to 1.17 hours. Individual C_{max} values ranged from 0.25 to 1.10 ng/mL. AUC_{0-24h} values ranged from 0.64 to 9.96 ng.h/mL, while AUC_{0-t} values ranged from 0.24 to 18.15 ng.h/mL. The concentration of everolimus was below the limit of quantification in all patients except for one at 72 hours. The C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination, $t_{½}$, AUC_{0-t}, AUC_{last}, $AUC_{0-\infty}$, and total blood clearance (CL) could also not be determined accurately due to rapid everolimus

disappearance from the blood. These types of results have been seen with other drug-eluting stents.

In summary, in the PLATINUM PK study, everolimus levels were below the detection limit at 72 hrs after stent implantation using an analytical method with a lower limit of quantification (LLOQ) of 0.20 ng/mL, except in one patient. These findings were confirmed in preclinical studies using multiple stents with total loaded doses above the clinically available stent system, where levels were undetectable after 72 hrs post implantation, Hence, in the absence of systemically detectable levels, standard pharmacokinetic parameters were not established.

Everolimus disappearance from circulation following PROMUS Element Stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, consistent local arterial delivery of everolimus from the stent has been demonstrated in pre-clinical studies.

B2. Drug Interactions

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with a cyclosporine (CsA). Formal drug interaction studies have not been performed with the PROMUS Element Stent because of limited systemic exposure to everolimus eluted from the stent. However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the PROMUS Element Stent in a patient taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism in vivo. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers [verapamil and diltiazem], aprepitant, atazanavir, nefazodone, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir and telithromycin
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, efavirenz, nevirapine, and dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- PgP inhibitors (digoxin, cyclosporine)
- Cisapride (theoretical potential interaction)

- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit/grapefruit juice

C. In Vitro Engineering Testing

In vitro engineering testing on the PROMUS Element Plus Stent System was conducted, as applicable, in accordance with:

- FDA Guidance for Industry: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010, and
- FDA Guidance for Industry and Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment, August 2008.

The in vitro engineering studies conducted are summarized in **Table 6**. "Pass" denotes that the test results met product specifications and/or the recommendation in the above-referenced guidance documents.

Additional testing was conducted to support the integrity of the coating on the PROMUS Element Stent as shown in **Section IX – D. Drug Coating Characterization Testing**.

For delivery system characterization testing, test articles used were devices identical to the commercial product for balloon characterization and Delivery, Deployment and Retraction testing, while delivery systems identical to those used in the clinical study were used for the other tests. Note that the only differences between the delivery systems used in the clinical study and the commercial devices are in the balloon.

Table 6: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Material Characterization		
Material Composition	Chemical analysis was conducted on the platinum chromium alloy (PtCr) and is provided by the material supplier to confirm both chemical analysis and inclusion/impurity content as provided by ASTM F138-00 "Standard Specification for Wrought 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)."	Pass
Stent Corrosion Resistance	Uncoated Element stents were tested to determine the corrosion susceptibility using cyclic potentiodynamic polarization per ASTM F2129-06,"Conducting Cyclic Potentiodynamic Polarization Measurements." Characterization of the crevice corrosion behavior of coated stents was performed similar to that described in ASTM F746-04, "Pitting or Crevice Corrosion of Metallic Surgical Implant Materials." Galvanic Corrosion characterization was performed when the Uncoated Element stent was overlapped with a stent of different metal/metal alloy per ASTM G71-81, "Conducting and Evaluation Galvanic Corrosion Tests in Electrolytes." Fretting Corrosion and Pitting and Crevice Corrosion was assessed on uncoated Element stents after pulsatile fatigue cycling. The corrosion series testing indicated that the corrosion resistance characteristics of the PROMUS Element Stent met product specification.	Pass
Dimensional Verification	To measure and inspect the Element stent to document that the stent dimensional specifications meet the product design requirements, including un-expanded stent dimensions, expanded diameter and length (see also Stent Delivery System Dimensional and Functional Attributes testing). All product met specifications.	Pass
Percent Surface Area	Stent surface coverage as a function of stent diameter was measured for the PROMUS Element Stent. The percent surface area is determined by dividing the measured total contact surface area of the coated stent by the surface area of the artery based on deployed stent measurements at the nominal stent diameter.	Pass
Foreshortening	The lengths of the stents were measured prior to and after expansion to nominal diameter. All stents met product specifications.	Pass
Recoil for Balloon Expandable Stents	Testing was conducted to quantify the amount of elastic recoil for the stent. Results indicated that product specifications were met for recoil of the stent.	Pass

Test	Description of Test	Conclusion
Stent Overexpansion	Testing was conducted to determine whether the deformation experienced by the stent undergoing expansion above the maximum rated diameter gives rise to stent or coating fractures. No stent exhibited any strut fracture when visually examined at 30X following overexpansion.	Pass
Radial Stiffness and Radial Strength	Testing was conducted to determine the ability of the PROMUS Element Stent to resist deformation under radial loads.	Pass
Compression Resistance	Testing was conducted to determine the radial resistance of the PROMUS Element Stent to external compression.	Pass
Mechanical Properties	Ultimate tensile strength, yield strength and elongation testing was performed on tubing (pre-processing) used to fabricate the stents. Ultimate tensile strength, yield strength and elongation on pre-processed tubing met product specification. Analysis of SEM images on stent components at various process stages determined that mechanical properties were not altered by processing.	Pass
Radiopacity	In vivo radiopacity of PROMUS Element Plus was performed using fluoroscopy in a porcine model during stent positioning, expansion and after the stent delivery system removal. Radiopacity of PROMUS Element Plus was found to be clinically acceptable in the swine model based on a blinded subjective assessment by the study Interventionalist.	Pass
Longitudinal Stiffness	Testing was conducted to determine the ability of the PROMUS Element Stent to resist deformation under axial compressive loads.	Characterization test / no acceptance criteria
Magnetic Resonance Imaging (MRI) Safety and Compatibility	The PROMUS Element Stent has been shown to be MR Conditional (poses no known hazards under specified conditions) through non-clinical testing of single and overlapped configurations up to 74 mm. The conditions are as follows: • Field strengths of 1.5 and 3 Tesla • Static magnetic field gradient <900 gauss/cm (extrapolated) • Normal operational mode (maximum whole body averaged specific absorption rate (SAR) of lower than 2.0 W/kg) for a total active MR scan time (with RF exposure) of 15 minutes or less The PROMUS Element Stent should not migrate in this MRI environment. MR imaging within these conditions may be performed immediately following the implantation of the stent. This stent has not been evaluated to determine if it is	Pass

Test	Description of Test	Conclusion
	MR Conditional beyond these conditions. 3.0 Tesla Temperature Information Non-clinical testing of RF-induced heating was performed at 123 MHz in a 3.0 Tesla Magnetom Trio®, Siemens Medical Solutions MR system, software version Numaris/4, Syngo® MR A30. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.2 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 74 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow. 1.5 Tesla Temperature Information Non-clinical testing of RF-induced heating was performed at 64 MHz in a 1.5 Tesla Intera® Philips Medical Systems, software version Release 10.6.2.0, 2006-03-10 whole body coil MR scanner. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.3 S/m. The phantom average SAR was calculated using calorimetry to be 2.1 W/kg. The maximal in-vitro temperature rise was calculated as 2.6°C for a measured stent length of 39 mm with the whole-body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow. In vivo, local SAR depends on MR Field strength and may be different than the estimated whole body averaged SAR, due to body composition, stent position within the imaging field, and scanner used, thereby affecting the actual temperature rise. Image Artifact Information The calculated image artifact extends approximately 7 mm from the perimeter of the device diameter and 5 mm beyond each end of the length of the stent when scanned in non-clinical testing using a Spin Echo sequence. With a Gradient Echo sequence the calculated image artifact extends 5 mm beyond the perimeter of the diameter and 6 mm beyond each end of the length with both sequences partially shielding the lumen in a 3.0 Tesla Intera (Achieva Upgrade), Philips Medical Solutions, software version Release 2.5.3.0 2007-09-28 MR system with a transmit/receive head coil.	

Test	Description of Test	Conclusion
	Medical Registration It is recommended that patients register the conditions under which the implant can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.	
Stent Delivery System Dimensional and Functional Attributes		
Delivery, Deployment and Retraction	The delivery, deployment and retraction of the PROMUS Element Plus Stent System was assessed by testing system track, crossing profile, deflated balloon profile, stent deployment, flexibility/kink, guidewire movement, torque strength, and balloon withdrawal from a stent and into the guide catheter. Testing demonstrated that the PROMUS Element Plus stent system could be delivered to the target location, deployed, and retracted, thus meeting required acceptance criteria.	Pass
Balloon Rated Burst Pressure (RBP)	PROMUS Element Plus Stent Systems were tested to failure to demonstrate that the stent system met rated burst pressure. All stent systems met specification and demonstrated with 95% confidence that at least 99.9% of balloons will not experience loss of integrity at or below the rated burst pressure.	Pass
Balloon Fatigue	PROMUS Element Plus Stent Systems across the range of stent/balloon lengths and diameters were required to complete 10 pressurization cycles to Rated Burst Pressure (RBP). The results show statistically that, with 95% confidence, 90% of the catheters will not experience balloon, shaft, or proximal/distal seal loss of integrity at or below the maximum recommended rated balloon burst pressure.	Pass
Stent Diameter vs. Balloon Pressure	Testing was performed to determine how the diameter of a deployed stent varies with applied balloon pressures. The stent sizing results verify that the stent systems meet the labeled compliance values.	Pass
Catheter Bond Strength	Representative sizes of the PROMUS Element Plus stent delivery system were tested to determine the balloon bond, tip bond, and full unit tensile strength of the delivery system. All stent systems exceeded the minimum specifications for full unit tensile strength and balloon bond.	Pass
Balloon Deflation Times	PROMUS Element Plus delivery systems across the range of balloon lengths and diameters were tested for deflation times, and all stent systems met specifications.	Pass
Stent	Testing was conducted to assess the forces required to	Pass

Test	Description of Test	Conclusion
Securement for Unsheathed Stents	displace a crimped PROMUS Element Stent from the delivery systems (1) directly from the delivery catheters, (2) after tracking through a simulated tortuous artery model and then through a simulated lesion. All stent systems met the stent securement specification.	
Non-Coaxial Withdrawal into a Simulated Guiding Catheter	Testing consists of withdrawing a catheter with a mounted stent non-coaxially into a simulated guide catheter tip following a track conditioning step in which the PROMUS Element Plus Stent Delivery Systems were challenged by repeatedly tracking the crimped stent system through a tortuous artery model. The unit was then assessed for stent movement. All samples met the specification.	Pass
Stent/Balloon Catheter Withdrawal Resistance	Testing was conducted to verify that the PROMUS Element Stent and deflated balloon system can be safely withdrawn back into the recommended guide catheter sizes both before and after stent deployment. All samples met the product specification.	Pass
Stent, System and Coating Durability Testing		
Acute Coating Integrity	The acute coating integrity of the PROMUS Element Stent coating was assessed via a series of acute in vitro tests performed on the coated stent (baseline and simulated use). The test results demonstrate that the PVDF-HFP/everolimus coating displays acceptable acute coating integrity.	Pass
Coating Adhesion and Cohesion	Coating adhesion and coating cohesion testing has been performed to assess the adhesive and cohesive properties of the PROMUS Element Stent coating. The PROMUS Element Plus coating demonstrates adequate adhesion and cohesion properties. The coating has a high resistance to detachment from the stent and is therefore considered acceptable for intended use.	Pass
Stress and Strain Analysis (Finite Element Analysis (FEA))	Using Finite Element Analysis (FEA), stress and strain analysis was performed on the stent and the stent coating to demonstrate that they maintain acceptable safety in stress loading environments, simulating nominal and overexpansion, and bending and radial conditions. The FEA evaluated the structural integrity of the stent and coating when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not occur over 400 million cycles (10-years) of loading.	Pass
Accelerated	Accelerated durability testing was performed on the	Pass

Test	Description of Test	Conclusion
Durability Testing	PROMUS Element Stent and the stent coating to demonstrate that the structural integrity and/or coating integrity is maintained following exposure to the pulsatile stresses and strains exceeding those typically experienced by a human coronary artery for 10 years (400 million cycles). Testing included assessment of Post-Elution Fatigue and Overlapping Pulsatile Fatigue on a Curve. All tested stents were free from fatigue induced strut fracture, and there was no evidence of coating integrity impact. The coated stent met the 10 year accelerated fatigue resistance specification.	
Particulate Testing	Particulate testing included assessment of Baseline Particulate (including Overexpansion), Simulated Use Particulate on the stent and delivery system, and Chronic Particulate overlapped on a curve following exposure to the pulsatile stresses and strains exceeding those typically experienced by a human coronary artery for 10 years (400 million cycles). The results demonstrate that the particulate counts are similar between PROMUS Element and ION stents, which in turn was similar to bare Element stents. Given comparable particulate counts, and that there is no evident increase in counts on PROMUS Element coated stent product, no chemical identification of particulates was warranted.	Pass

D. Drug Coating Characterization Testing

The coating characterization testing conducted on the PROMUS Element Stent coating is summarized in **Table 7**.

Table 7: Coating Characterization Testing

Test	Description of Test
Materials Analysis – Polymer	Polymer components were tested to ensure conformity to raw material specifications. The analysis confirmed the material met specifications.
Chemical Analysis-Polymer	Assays were conducted to determine Mw, polydispersity, and monomer content. The results of each assay met specifications established by the applicant.
Chemical Analysis - Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis (COA); the testing confirmed conformity to the COA.
Drug Loading Density	Dose per unit area was calculated.
Coating Thickness Uniformity	Testing was conducted to verify the adluminal/abluminal/sidewall coating thickness uniformity along the stent, from stent to stent and batch to batch.
Coating Adhesion/Cohesion	Coating Adhesion and Cohesion testing was conducted to assess the adhesive and cohesive properties of the PROMUS Element Stent coating.
Drug Content	Assay was conducted to quantitatively determine the total amount of the drug substance, everolimus, on the PROMUS Element Stent.
Impurities and Degradation Products	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the PROMUS Element Stent.
In Vitro Elution	Assay was developed to measure the in vitro release kinetics of everolimus from the PROMUS Element Stent.
Particulates	Particulate levels were evaluated for the PROMUS Element Plus stent system under simulated use conditions, including tracking and deployment (see Table 5 above).

Chemistry Manufacturing and Controls (CMC) Testing

Each batch of finished devices undergoes CMC testing. This testing is summarized in **Table 8**. Where applicable, the test methods follow International Conference on Harmonization (ICH) Guidelines. Information to support the stability of PROMUS Element Plus is summarized separately in **Section IX – E. Stability**.

Table 8: CMC Release Testing

Test	Description of Test
Material Analysis - Polymer	The polymers are tested to ensure conformity to specifications. The polymers must meet specifications prior to utilization in finished goods.
Drug Identity	Assay is conducted to verify the identity of the drug substance, everolimus, in the PROMUS Element Stent.
Drug Content/Content Uniformity	Multiple stents are assayed to verify the uniformity of the drug content between individual stents is within specifications established for the PROMUS Element Stent.
Impurities and Degradation Products	Testing is conducted to quantitatively verify amount of impurities and degradation products on the PROMUS Element Stent are within the specifications established for the PROMUS Element Stent.
In Vitro Drug Elution	The in vitro release profile of everolimus is measured to verify that the drug release is within the specifications established for the PROMUS Element Stent.
Particulates	Particulate counts are measured to verify that they remain below acceptable levels established for the PROMUS Element Stent.
Endotoxin	Testing is conducted to quantitatively verify endotoxin on the PROMUS Element Stent are within the specifications established for the PROMUS Element Stent.

E. Stability

Stability studies were conducted to establish a shelf life/expiration date for PROMUS Element Plus. The stability testing evaluation included appearance, drug content assay, drug content uniformity, drug identity, residual solvents, impurities and degradants, in vitro elution, particulates, sterility, and endotoxin. Appropriate mechanical engineering tests were also performed on aged product and packaging to ensure that PROMUS Element Plus continues to meet specification throughout its shelf life. The data generated supports a shelf life of 12 months. In addition, the stability of the drug substance and inactive polymers has been independently verified.

F. Sterilization

The PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) is sterilized using ethylene oxide sterilization and has been validated per AAMI/ISO 11135-1: 2007 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The amount of bacterial endotoxin was verified to be within the specification limit of 20EU/device for PROMUS Element Plus stent delivery systems.

Packaging shelf-life testing supports a shelf life of up to 19 months.

G. Animal Studies

Because detailed arterial histopathology and histomorphometry and pharmacokinetic data cannot be obtained through human clinical trials, a series of animal studies were conducted to evaluate safety, vascular compatibility, in vivo drug release, and acute product performance.

The safety, vascular compatibility, and acute performance of PROMUS Element Everolimus-Eluting Stent were evaluated in the non-injured porcine coronary artery model in Study 07-032G. This nonclinical animal testing also assessed comparability between PROMUS Element and PROMUS® (Xience® V), Polymer Only coated Element stents, and Uncoated Element stents. The results of these tests support the safety and vascular compatibility of the PROMUS Element stent in single and overlap-stent implant configurations in the non-injured porcine coronary artery. The early and late tissue responses were similar to PROMUS® (Xience® V). In addition, acute performance of PROMUS Element was found to be the same as or better than PROMUS® (Xience® V), supporting the safety of the PROMUS Element stent system.

Additionally, similar in vitro and in vivo drug release profiles and local arterial tissue concentration profiles between PROMUS Element and PROMUS® (Xience® V) were demonstrated through the nonclinical pharmacokinetic study, Study 07-036G. PROMUS Element in vivo everolimus release and tissue everolimus levels were evaluated and compared with PROMUS® (Xience® V) using the porcine coronary artery model. Furthermore, fast and slow drug release formulations of PROMUS Element were included in this study for the development and validation of in vitro-in vivo correlation (IVIVC) models.

In addition to conducting these GLP studies, previous studies completed for the PROMUS® (Xience® V) Everolimus Eluting Coronary Stent System also support the PROMUS Element Plus product. For more details on these studies, please refer to the SSED for PROMUS® / Xience® V stents located: http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf Summaries of all animal studies are included in **Table 9**. Studies were conducted in accordance with §21 CFR 58 (Good Laboratory Practices), except one study on PROMUS® (Xience® V) where a rationale was provided to demonstrate that appropriate animal care procedures were followed and data integrity was maintained.

Table 9: Summary of the Major Supportive Animal Studies

Study Number	Stent Design	Drug Loading Density (µg/cm^2) / (Drug: Polymer w/w)[a]	Type/# of Animals	Vessel Location	Evaluation Time Points	Endpoints
GLP Safety Overlap Study 07-032G GLP: Yes	Test Article: PROMUS Element 3.00 x 8 mm 3.50 x 8 mm (53 pairs histology, 9 pairs SEM)	100 / 1:4.9	Swine, 79	LAD, RCA, and/or LCX	7, 30, 90, 180, 270 Days	• Morbidity, mortality, stent thrombosis, Myocardial Infarction (MI) • Angiographic vessel patency • Visual analysis of fracture • Histological vascular response • SEM • Morphological and morphometric parameters • Acute device handling and deliverability
	Control Articles: Polymer Only Element 3.00 x 8 mm 3.50 x 8 mm (46 pairs histology, 9 pairs SEM)	N/A				
	Element Bare 3.00 x 8 mm 3.50 x 8 mm (45 pairs histology, 9 pairs SEM)	N/A				
	PROMUS (Xience V) 3.00 x 8 mm 3.50 x 8 mm (47 pairs histology, 9 pairs SEM)	100 / 1:4.9				
Dosing Study R-040703-CW-02 GLP: No	Test Articles: PROMUS (Xience V) 3.00 X 12 mm 3.00 X 12 mm (11 histology)	100 / 1:4.9	Swine, 19	RCA, LAD, and/or LCX	28 days	Evaluation of dose response of various everolimus formulations. • Angiography • Histological & histomorphometric evaluations • Evaluation of degree of endothelialization by SEM • Acute delivery • Chronic vascular response • Dosing study (B;A=1.3:1.0)
	PROMUS (Xience V) 3.00 X 12 mm 3.00 X 12 mm (11 histology)	200 / 1:3				
	PROMUS (Xience V) 3.00 X 12 mm (11 histology)	260 / 1:4				
	Control Article: Vision Bare (11 histology)	N/A – Bare stent				

Study Number	Stent Design	Drug Loading Density ($\mu g/cm^2$) / (Drug: Polymer w/w)[a]	Type/# of Animals	Vessel Location	Evaluation Time Points	Endpoints
Max Dose Study R051503-DMH GLP: Yes	Test Article: PROMUS (Xience V) 3.00 x 12 mm (11 histology, 1 SEM)	803 / 1:1.42	Swine, 14	RCA, LAD, and/or LCX	28 days	Evaluation of maximum dose everolimus and bulk polymer. • Angiography • Histological & histomorphometric evaluations • Evaluation of degree of endothelialization by SEM • Acute delivery • Chronic vascular response
	Control Articles: Polymer Only Vision stent 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Polymer Only				
	Vision Bare 3.00 x 12 mm (11 histology)	N/A – Bare stent				
Max Dose Study R050503-DMH GLP: Yes	Test Articles: PROMUS (Xience V) 3.00 x 12 mm (11 histology, 1 SEM)	803 / 1:1.42	Swine, 14	RCA, LAD, and/or LCX	90 days	Evaluation of maximum dose everolimus and bulk polymer. • Angiography • Histological & histomorphometric evaluations • Evaluation of degree of endothelialization by SEM • Acute delivery • Chronic vascular response
	Control Articles: Polymer Only Vision stent 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Polymer only				
	Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				
Max Dose Study R032204-PDD GLP: Yes	Test Article: PROMUS (Xience V) 3.00 x 12 mm (11 histology, 1 SEM)	803 / 1:1.42	Swine, 13	RCA, LAD, RCA LAD, and/or LCX	180 days	Evaluation of maximum dose everolimus and bulk polymer. • Angiography • Histological & histomorphometric

Study Number	Stent Design	Drug Loading Density ($\mu g/cm^2$) / (Drug: Polymer w/w)[a]	Type/# of Animals	Vessel Location	Evaluation Time Points	Endpoints
	Control Articles: Polymer Only Vision stent 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Polymer only				evaluations • Evaluation of degree of endothelialization by SEM • Acute delivery • Chronic vascular response
	Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				
Safety Study R050304-PDD Part II GLP: Yes	Test Article: PROMUS (Xience V) 3.00 x12 mm (11 histology, 1 SEM)	100 / 1:4.9	Swine, 6	RCA LAD, RCA LAD, and/or LCX	2 years	• Angiography • Histological & histomorphometric evaluations • Acute delivery • Chronic vascular response
	Control Article: Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				
Polymer Safety Study R050504-KHB Part II GLP: Yes	Test Article: Polymer Only Vision stent 3.00 x 12 mm (5 histology)	N/A – Polymer only	Swine, 5	RCA LAD, RCA LAD, and/or LCX	2 years	Evaluation of polymer safety • Angiography • Histological & histomorphometric evaluations • Acute delivery • Chronic vascular response
	Control Article: Vision Bare 3.00 x 12 mm (5 histology)	N/A – Bare stent				

Study Number	Stent Design	Drug Loading Density ($\mu g/cm^2$) / (Drug: Polymer w/w)[a]	Type/# of Animals	Vessel Location	Evaluation Time Points	Endpoints
R051004-MJL GLP: Yes	Test Article: PROMUS (Xience V) 3.00 x 12 mm (54, 6 per time point)	100 / 1:4.9	Swine, 18	RCA, LAD, and/or LCX	Blood: 15, 30, 45, 60, 90, 120, 150, 180 min, 6 and 12 hours Others: 3, 6 and 24 hours, 3,14,28, 60,90,120 days	Evaluation of % drug released, arterial and other tissue drug levels & systemic blood levels over time.
In Vivo PK Study 07-036G GLP: Yes	Test Articles: PROMUS Element (Nominal Release) 3.00 x 8 mm 3.50 x 8 mm (107 stents tissue and 18 stents coating integrity)	100 / 1:4.9	Swine, 147	LAD, RCA, LCX	3, 6 hours, 1, 3, 7, 10, 14, 28, 60, 90 days	Arterial tissue levels of Everolimus + residual stent content • 3 hrs, 6 hrs, 1, 3, 7, 10, 14, 28, 60, 90 days time pts Tissues sampled: • Proximal unstented coronary artery • Stented coronary artery • Distal unstented coronary artery • Control - uninjured carotid artery • Kidney, liver, myocardium, spleen, and lung Blood levels (everolimus) at: • 15 min, 30 min, and 1, 2, 4, 6, 8, 24, 48 and 72 hours
	PROMUS Element (Slow Release) 3.00 x 8 mm 3.50 x 8 mm (105 total stents)	100 / 1:5.5				
	PROMUS Element (Fast Release) 3.00 x 8 mm 3.50 x 8 mm (105 total stents)	100 / 1:4.3				
	Control Article: PROMUS (Xience V) 3.00 x 8 mm (105 total stents)	100 / 1:4.9				
R050203-MJL GLP: Yes	Test Articles: PROMUS (Xience V) 3.00 x 12 mm (42, 6 per time point)	100 / 1:4.9	Swine, 51	RCA, LAD, and/or LCX	0.25, 1, 3, 7, 14, 28, 60 days	Determination of everolimus in: • coronary/ carotid artery • kidney • liver

Study Number	Stent Design	Drug Loading Density ($\mu g/cm^2$) / (Drug: Polymer w/w)[a]	Type/# of Animals	Vessel Location	Evaluation Time Points	Endpoints
	PROMUS (Xience V) 3.00 x 12 mm (54, 6 per time point)	200 / 1:3			0.25, 1, 3, 7, 14, 28, 60, 90, 120 days	• lung • myocardium • spleen System characterized in terms of drug release and tissue concentration levels.
	PROMUS (Xience V) 3.00 x 12 mm (54, 6 per time point)	260 / 1:4			0.25, 1, 3, 7, 14, 28, 60, 90, 120 days	
R0060228-MJL (Platelet Function, Max Dose PK) GLP: Yes	Test Article: PROMUS (Xience V) 3.00 x 12 mm (36, 4-6 per time point)	803 / 1:1.42	Swine, 32	RCA, LAD, and/or LCX	Blood Levels: 15, 30, 45, 60, 90, 120, 150, 180 min, 6 and 12 hours Others: 3, 6 and 24 hours, 3, 14, 28, 60 days Platelet Function: 1, 3, 7, and 14 days	Evaluate the effect of high dose everolimus eluting stents on platelet function and to evaluate the systemic exposure of everolimus following stent-based delivery of >700 µg of everolimus by determining the concentration of everolimus in blood and selected key organs.

Note: The stent delivery system used in these animal studies was identical to the devices used in the PLATINUM series of clinical trials, but is slightly different from commercial product. The commercial product utilizes a stent delivery system that consists of the identical materials and similar design and processing to that of the ION Paclitaxel-Eluting Platinum Chromium Coronary Stent System (P100023).

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant collected clinical data through the PLATINUM Clinical Trial Program, to establish a reasonable assurance of safety and effectiveness of coronary artery stenting with the PROMUS Element stent for improving luminal diameter in patients with symptomatic heart disease due to de novo lesions in native coronary arteries. The PLATINUM Trial program consisted of a workhorse (WH) randomized controlled trial (RCT) with single-arm small vessel (SV), long lesion (LL), and pharmacokinetics (PK) sub-studies, and the PLATINUM quantitative coronary angiography (QCA) study. Note that the LL study data were not included in this

submission. The PLATINUM WH trial included sites in the United States, Europe, Japan, and the Asia-Pacific region excluding Japan. The PLATINUM SV trial included sites in Australia, Belgium, France, Japan, and New Zealand. Both trials were evaluated under IDE G080202. The intent of the PK sub-study was to confirm that the PK parameters measured following implantation of the PROMUS Element device were consistent with prior studies conducted with the PROMUS® (Xience® V) device. Refer to **Section IX – B. In Vivo Pharmacokinetics** for results.

The PLATINUM QCA study was conducted at clinical sites in Australia, Malaysia, New Zealand, and Singapore. A summary of the trial design and results are provided in **Section X - C. PLATINUM QCA**.

Data from the PLATINUM Clinical Trial Program were the basis for the PMA approval decision. A summary of the WH, SV, PK and QCA trial designs is presented in **Table 10**.

Table 10: Comparison of PLATINUM Clinical Studies

	PLATINUM			PLATINUM QCA
	Workhorse RCT	**Small Vessel**	**PK**	
Purpose	Evaluation of safety and effectiveness in workhorse lesions	Evaluation of safety and effectiveness in small vessel lesions	Evaluation of everolimus blood levels	Evaluation of angiographic and IVUS outcomes
Study Design	Prospective, randomized, controlled, multi-center, single-blind non-inferiority to PROMUS	Prospective, single arm, multicenter, comparison to performance goal	Prospective, single arm, multicenter, observational	Prospective, single arm, multicenter, observational; comparisons of two efficacy endpoints to performance goals
Primary Endpoint	12M TLF	12M TLF	N/A, observational	30D composite rate (cardiac death, MI, TLR, ST)
Number of Patients (ITT)	1530 enrolled; PROMUS Element: 768 PROMUS: 762	94 PROMUS Element	22 PROMUS Element	100 PROMUS Element
Polymer	PBMA, PVDF-HFP			
Everolimus Dose Density	100 $\mu g/cm^2$			
Lesion Criteria: Vessel Diameter (by visual estimate), mm	≥2.50 to ≤4.25	≥2.25 to <2.50	≥2.50 to ≤4.25	≥2.25 to ≤4.25
Lesion Criteria: Lesion Length (by visual estimate), mm	≤24	≤28	≤24	≤34
Total Target Lesions	Up to 2	1	Up to 2	1
Stent Matrix	2.50-4.00 mm diameter 12, 18/20[1], 28 mm length	2.25 mm diameter 12, 20, 28, 32 mm length	2.50-4.00 mm diameter 12, 20, 28 mm length	2.25-4.00 mm diameter 12, 20, 28, 32, 38[2] mm length
Post-Procedure Antiplatelet Therapy	Thienopyridine: at least 6 months, ideally for 12 months in patients not at high risk of bleeding; ASA: indefinitely			
Follow-Up	Clinical: 30 days, 6 months, 1 year, 18 months, annually 2-5 years			Clinical: 30 day, 9 month, 1 year;

Table 10: Comparison of PLATINUM Clinical Studies

	PLATINUM			PLATINUM QCA
	Workhorse RCT	Small Vessel	PK	
				Angiographic: 9 month; IVUS: 9 month

[1]PROMUS available in 18 mm length; PROMUS Element available in 20 mm length.
[2]2.25 mm stent not available in 38 mm length.
Abbreviations: ASA=aspirin; ITT=intent-to-treat; IVUS=intravascular ultrasound; MI=myocardial infarction; PK=pharmacokinetics; PBMA=poly (n-butyl methacrylate); PVDF-HFP=poly (vinylidene fluoride-co-hexafluoropropylene); QCA=quantitative coronary angiography; RCT=randomized controlled trial; ST=stent thrombosis; TLF=target lesion failure; TLR=target lesion revascularization

A. PLATINUM Workhorse

Primary Objective: The objective of the study is to evaluate the safety and effectiveness of the PROMUS Element Everolimus-Eluting Coronary Stent for the treatment of patients with up to two de novo atherosclerotic coronary artery lesions.

Design
The PLATINUM Workhorse (WH) study is a prospective, randomized, controlled, single-blind, multi-center non-inferiority trial designed to evaluate the PROMUS Element Everolimus-Eluting Platinum Chromium Coronary Stent System in the treatment of *de novo* coronary lesions. The trial employs a 1:1 randomization to the PROMUS Element (test) or the PROMUS® (control) everolimus-eluting stent. The primary endpoint is 12-month target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion (TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death related to the target vessel.
Eligible patients were those ≥18 years old with left ventricular ejection fraction (LVEF) ≥30% and with documented stable angina pectoris, silent ischemia, or unstable angina pectoris. *De novo* target lesions in a native coronary artery with diameter stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1, reference vessel diameter (RVD) ≥2.50 mm and ≤4.25 mm (visual estimate), and lesion length ≤24 mm (visual estimate) were eligible. Patients could be treated for 1 or 2 target lesions. Patients treated for a single target lesion could also have 1 de novo native coronary artery lesion within a different epicardial vessel (non-target lesion) treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure. The non-target lesion had to be treated before the target lesion and the treatment had to be a clinical angiographic success (defined as visually assessed <50% [<30% for stents] with TIMI 3 flow without prolonged chest pain or electrocardiogram [ECG] changes consistent with myocardial infarction [MI]) before the patient could be enrolled. Patients were to have provided written informed consent. Randomization was stratified by the presence or absence of diabetes mellitus treated with medication(s), by the intent to treat 1 versus 2 target lesions, and by study site. A complete list of inclusion and exclusion criteria follows. This list is applicable to the SV sub-study as well, which is summarized in

Section X (B1) – PLATINUM Small Vessel, Clinical Study Design.

Clinical Inclusion Criteria	• Patient must be at least 18 years of age • Patient (or legal guardian) understands the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed • For patients less than 20 years of age enrolled at a Japanese site, the patient and the patient's legal representative must provide written informed consent before any study-specific tests or procedures are performed • Patient is eligible for percutaneous coronary intervention (PCI) • Patient has documented stable angina pectoris or documented silent ischemia; or unstable angina pectoris • Patient is an acceptable candidate for coronary artery bypass grafting (CABG) • Patient has a left ventricular ejection fraction (LVEF) ≥30% as measured within 30 days prior to enrollment • Patient is willing to comply with all protocol-required follow-up evaluations
Angiographic Inclusion Criteria (visual estimate)	• Target lesion must be a de novo lesion located in a native coronary artery with a visually estimated RVD as follows: o ≥2.50 mm and ≤4.25 mm for the RCT (WH selection criteria) o ≥2.25 mm and <2.50 mm for the non-randomized SV subtrial (SV selection criteria) • Target lesion length must measure (by visual estimate) as follows. o ≤24 mm for the RCT (WH selection criteria) o ≤28 mm for the non-randomized SV subtrial (SV selection criteria) • Target lesion must be in a major coronary artery or branch with visually estimated stenosis ≥50% and <100% with TIMI flow >1
Clinical Exclusion Criteria	• Patient has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute MI • Patient has had a known diagnosis of recent MI (i.e., within 72 hours prior to the index procedure) and has elevated enzymes at the time of the index procedure as follows: o Patients are excluded if any of the following criteria are met at the time of the index procedure: o If CK-MB >2× upper limit of normal (ULN), the patient is excluded regardless of the CK Total o If CK-MB is 1-2× ULN, the patient is excluded if the CK Total is >2× ULN o If CK Total/CK-MB are not used and Troponin is, patients are excluded if the following criterion is met at the time of the index procedure. o Troponin >1× ULN with at least one of the following: o Patient has ischemic symptoms and ECG changes indicative of ongoing ischemia (e.g., >1 mm ST segment

	elevation or depression in consecutive leads or new left bundle branch block [LBBB]); o Development of pathological Q-waves in the ECG; or o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality *Note*: For patients with unstable angina or patients who have had a recent MI, CK Total/CK-MB (or Troponin if CK Total/CK-MB are not used) must be documented prior to enrolling/randomizing the patient • Patient has received an organ transplant or is on a waiting list for an organ transplant • Patient is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure • Patient is receiving oral or intravenous immunosuppressive therapy (i.e., inhaled steroids are not excluded) or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus, but not including diabetes mellitus) • Patient is receiving chronic (≥72 hours) anticoagulation therapy (e.g., heparin, coumadin) for indications other than acute coronary syndrome • Patient has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 • Patient has a white blood cell (WBC) count <3,000 cells/mm^3 • Patient has documented or suspected liver disease, including laboratory evidence of hepatitis • Patient is on dialysis or has known renal insufficiency (i.e., estimated creatinine clearance <50 ml/min by the Cockcroft Gault formula: [(140-age)*lean body weight (in kg)]/[plasma creatinine (mg/dl)*72]) • Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions • Patient has had a cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months, or has any permanent neurologic defect that may cause non-compliance with the protocol • Target vessel(s) or side branch has been treated with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) within 12 months prior to the index procedure • Target vessel(s) has been treated within 10 mm proximal or distal to the target lesion (by visual estimate) with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) at any time prior to the index procedure • Non-target vessel or side branch has been treated with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) within 24 hours prior to the index procedure • Planned or actual target vessel(s) treatment with an unapproved device, directional or rotational coronary atherectomy, laser, cutting

	balloon, or transluminal extraction catheter immediately prior to stent placement • Planned PCI or CABG after the index procedure • Patient previously treated at any time with coronary intravascular brachytherapy • Patient has a known allergy to the study stent system or protocol-required concomitant medications (e.g., stainless steel, platinum, cobalt, chromium, nickel, tungsten, acrylic, fluoropolymers, everolimus, thienopyridines, aspirin, contrast) that cannot be adequately premedicated • Patient has an active peptic ulcer or active gastrointestinal (GI) bleeding • Patient has one of the following. o Other serious medical illness (e.g., cancer, congestive heart failure) that may reduce life expectancy to less than 24 months o Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) o Planned procedure that may cause non-compliance with the protocol or confound data interpretation • Patient is participating in another investigational drug or device clinical trial that has not reached its primary endpoint • Patient intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure • Patient with known intention to procreate within 12 months after the index procedure (Women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure.) • Patient is a woman who is pregnant or nursing (A pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential.) • WH patient has more than 2 target lesions, or more than 1 target lesion and 1 non-target lesion, which will be treated during the index procedure • SV patient has more than 1 target lesion, or more than 1 target lesion and 1 non-target lesion, which will be treated during the index procedure
Angiographic Exclusion Criteria (visual estimate)	• Target lesion meets any of the following criteria: o Aorto-ostial location (i.e., lesion located within 5 mm of the ostium by visual estimate) o Left main location o Located within 5 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCX) coronary artery by visual estimate o Located within a saphenous vein graft or an arterial graft o Will be accessed via a saphenous vein graft or an arterial graft o Involves a side branch ≥2.0 mm in diameter by visual estimate

	○ Involves a clinically significant side branch <2.0 mm in diameter by visual estimate that has a clinically significant stenosis at the ostium ○ TIMI flow 0 (total occlusion) or TIMI flow 1 prior to wire crossing ○ Excessive tortuosity proximal to or within the lesion ○ Extreme angulation proximal to or within the lesion ○ Target lesion and/or target vessel proximal to the target lesion is moderately to severely calcified by visual estimate ○ Restenotic from previous intervention ○ Thrombus, or possible thrombus, present in the target vessel • Non-target lesion to be treated during the index procedure meets any of the following criteria: ○ Located within the target vessel ○ Located within a bypass graft (venous or arterial) ○ Left main location ○ Chronic total occlusion ○ Involves a complex bifurcation (e.g., bifurcations requiring treatment with more than 1 stent) ○ Restenotic from previous intervention • Patient has unprotected left main coronary artery disease (>50% diameter stenosis) • Patient has protected left main coronary artery disease and a target lesion in the LAD or LCX • Patient has an additional clinically significant lesion(s) in the target vessel for which an intervention within 12 months after the index procedure is likely to be required • Patient has 2 target lesions in the same vessel that are separated by less than 15 mm (by visual estimate) ***Note:*** Multiple focal stenoses will be considered as a single lesion if they can be completely covered with 1 stent.

After hospital discharge, enrolled patients are to undergo clinical follow-up at 30 days, 6 months, 12 months, 18 months, 2 years, and annually to 5 years post-index procedure. Starting with the 18-month visit, follow-up will be limited to the safety analysis set, which is composed of all study patients who received a study stent (PROMUS® or PROMUS Element). Follow-up is complete through 1 year, the timing at which the primary endpoint for the trial was assessed, with additional follow-up ongoing. Regarding antiplatelet therapy, the protocol mandated compliance with the ACC/AHA/SCAI Guidelines for PCI[1].

An angiographic core lab was utilized for analysis of angiography data. A Clinical Events Committee (CEC) served as a multidisciplinary expert group responsible for the independent and ongoing adjudication of prespecified clinical events, including all reported deaths, myocardial infarctions (MI), target vessel revascularizations (TVR), and stent thromboses (ST), as defined by the clinical protocol. A Data Monitoring Committee (DMC) of independent experts in

cardiology, cardiovascular interventional therapy, and biostatistics worked to ensure patient safety by evaluating accumulating data from the PLATINUM Clinical Program.
Baseline, procedural, and follow-up data were summarized using descriptive statistics for continuous variables and frequency tables or proportions for discrete variables. Treatment groups were compared with a two sided chi-square or Fisher exact test for discrete variables and Student *t*-test for continuous variables. Estimates of treatment difference were reported as relative risk and absolute difference with 95% confidence intervals of differences provided. All analyses of proportions were based on patients with sufficient follow-up. The Kaplan-Meier product-limit method was used to estimate event rates for time-to-event outcomes; treatment groups were compared using log-rank and Wilcoxon tests. Endpoints were analyzed using 2 populations: intent-to-treat (ITT, N=1530) and per-protocol (N=1503, includes only patients who received the assigned study stent). Univariate and multivariate analyses were performed to assess possible predictors of the primary endpoint (12-month TLF).

Clinical Endpoints

The primary endpoint is the 12-month rate of TLF, defined as any ischemia-driven revascularization of the target lesion, MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death related to the target vessel. Myocardial infarction is defined and reported according to the PLATINUM definition, SPIRIT III definition (P070015), and Academic Research Consortium definition; the PLATINUM definition for MI is used for the primary endpoint. The definition of MI is as follows:

Periprocedural MI (i.e., MI occurring within 48 hours of the index procedure or any repeat revascularization):

- Q-Wave MI: Development of new (i.e., not present on the patient's ECG before allocation) pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with postprocedure CK-MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1× >ULN and the baseline level must have been <ULN.
- Non–Q-Wave MI: De novo elevation of CK Total levels >3.0× ULN without the presence of new Q-waves (i.e., not present on the patient's ECG before allocation). If CK-MB is performed, it must be positive. In the absence of either CK or CK-MB, Troponin may be used and must be 3× >ULN and the baseline level must have been <ULN. There must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

For patients undergoing bypass surgery, a perioperative MI will be defined as follows.

- Total CK-MB >5× ULN. If no CK-MB is available, Troponin may be used. It must be >5× ULN, the baseline level must have been <ULN, and there must be evidence of any one of the following: new LBBB or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium, OR
- Presence of new pathologic Q-waves as defined above.

Spontaneous MI:

- Q-Wave MI: Development of new (i.e., not present on the patient's ECG before allocation) pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with postprocedure CK-MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1× >ULN and the baseline level must have been <ULN.
- Non–Q-Wave MI: De novo elevation of CK Total levels >2.0× ULN without the presence of new Q-waves (i.e., not present on the patients ECG before allocation). If CK-MB is performed, it must be positive. In the absence of either CK or CK-MB, Troponin may be used and must be 2× >ULN and the baseline level must have been <ULN. There must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), or imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

A one-sided Farrington-Manning test was used to test the hypothesis that the primary endpoint rate in the PROMUS Element arm is non-inferior to the rate in the PROMUS arm, within a margin of 3.5%.

Other key secondary endpoints included the following:

Additional efficacy endpoints (in-hospital, 30 days, 6 months, 12 months, 18 months, 2–5 years):

- TLR rate
- TLF rate (*primary endpoint at 12 months for RCT and SV and LL subtrials*)
- Target vessel revascularization (TVR) rate
- Target vessel failure (TVF) rate

Additional Safety endpoints (in-hospital, 30 days, 6 months, 12 months, 18 months, 2–5 years):

- MI (Q-wave and non–Q-wave) rate
- Cardiac death rate
- Non-cardiac death rate
- All death rate
- Cardiac death or MI rate
- All death or MI rate
- All death/MI/TVR rate
- Stent thrombosis rate (definite or probable by ARC definitions)

A1. Accountability of PMA Cohort

A total of 1530 patients (762 PROMUS® and 768 PROMUS Element) were enrolled and randomized at 132 clinical sites from January 27, 2009 to September 4, 2009. Of these, 788 patients were from the USA, 562 from Europe, 124 from Japan, and 56 from the Asia-Pacific region excluding Japan. Of the 1530 patients included in the intent-to-treat analysis set, a total of 1469 patients (727 PROMUS® and 742 PROMUS Element) were evaluable for the primary endpoint of 12-month TLF. Patient disposition for the ITT analysis set is shown in **Table 11**.

Table 11: Patient Disposition for PLATINUM WH Study, ITT, All Patients (N=1530)

Category	PROMUS Stent (N=762)	PROMUS Element Stent (N=768)
Intent-to-treat analysis set	762	768
Death ≤395 days, no 12-month clinical follow-up performed	8	10
Eligible for 12-month clinical follow-up[1]	754	758
12-month clinical follow-up performed[2]	96.4% (727/754)	97.0% (735/758)
Office visit	650	665
Telephone contact	77	70
No 12-month clinical follow-up performed	27	23
Prematurely discontinued	6	2
Death > 395 days	0	0
Withdrew consent	6	1
Lost to follow-up	0	0
Adverse event	0	0
Investigator discretion	0	0
Transplant or removal of target organ	0	0
Other[3]	0	1
Missed 12-month visit	21	21
With later follow-up visit performed	1	4
No later follow-up visit performed	20	17
12-month clinical follow-up or death[4]	96.5% (735/762)	97.0% (745/768)
12-month clinical follow-up patient accountability[5]	95.4% (727/762)	95.7% (735/768)

Numbers are counts of patients or % (count/sample size).
1: Patients who died prior to completion of follow-up window and prior to completing a 12-month clinical follow-up visit are considered censored and are excluded from calculation of proportion of patients who completed clinical follow-up visit.
2: Based on patients eligible for 12-month clinical follow-up
3: Patient incarcerated
4: Includes patients who have died in both the numerator and the denominator; based on the ITT analysis set
5: All patients with 12-month follow-up out of all ITT patients
Abbreviation: ITT=intent-to-treat

A2. Study Population Demographics and Baseline Parameters

Table 12 presents baseline demographic and clinical characteristics, by treatment group, for the ITT analysis set (N=1530). Patients were well-matched for baseline demographics. Average age was 64.0±10.3 and 63.1±10.3 in the PROMUS Element and PROMUS® stent groups, respectively. Approximately 72% of patients in the PROMUS Element stent group and 71% of patients the PROMUS stent group were male, and 22% of patients in the PROMUS Element group and 25% in the PROMUS® stent group were medically treated diabetics.

Table 12: Baseline Demographic and Clinical Characteristics, ITT, All Patients (N=1530)

Parameter	PROMUS Stent (N=762)	PROMUS Element Stent (N=768)
Male	71.1% (542/762)	71.6% (550/768)
Age (years)	63.11±10.28 (762) (32.00, 90.00)	63.99±10.27 (768) (27.00, 94.00)
Ethnicity and Race		
American Indian or Alaska native	0.5% (4/762)	0.4% (3/768)
Asian	8.9% (68/762)	9.8% (75/768)
Black, of African heritage	2.8% (21/762)	2.3% (18/768)
Caucasian	84.5% (644/762)	84.6% (650/768)
Hispanic or Latino	2.0% (15/762)	1.7% (13/768)
Maori	0.0% (0/762)	0.1% (1/768)
Native Hawaiian or other Pacific Islander	0.5% (4/762)	0.4% (3/768)
Other	0.1% (1/762)	0.4% (3/768)
Not disclosed	0.8% (6/762)	0.7% (5/768)
General Medical History		
Smoking, ever	60.5% (448/741)	65.6% (493/751)
Current	17.7% (131/741)	21.0% (158/751)
Previous	42.8% (317/741)	44.6% (335/751)
Diabetes[1]	25.1% (191/762)	22.0% (169/768)
Insulin	6.3% (48/762)	7.7% (59/768)
Oral (no insulin)	18.8% (143/762)	14.3% (110/768)
Diabetes treated with diet only	2.0% (15/762)	4.6% (35/768)
Hyperlipidemia[1]	76.2% (579/760)	78.2% (598/765)
Hypertension[1]	73.2% (558/762)	70.9% (544/767)
History of bleeding disorder	1.2% (9/757)	1.8% (14/763)
Gastrointestinal	1.1% (8/757)	1.3% (10/763)
Hematologic dyscrasia	0.3% (2/757)	0.7% (5/763)
Cardiac History		
Angina, stable	60.8% (463/762)	61.8% (474/767)
Angina, unstable	24.7% (188/762)	24.1% (185/767)
Silent ischemia	19.2% (143/743)	17.2% (128/744)
Family history of CAD	56.6% (401/709)	55.4% (392/708)
Previous MI	21.1% (160/760)	21.0% (160/761)
LVEF (%)	59.04±9.54 (741) (30.00, 90.00)	59.53±10.07 (745) (30.00, 90.00)
Neurologic, Renal, and Peripheral History		
TIA or CVA	4.6% (35/757)	6.9% (53/767)
TIA	1.7% (13/757)	4.0% (31/768)
CVA	3.0% (23/759)	3.5% (27/767)
Renal disease	3.0% (23/759)	3.4% (26/767)

Table 12: Baseline Demographic and Clinical Characteristics, ITT, All Patients (N=1530)

Parameter	PROMUS Stent (N=762)	PROMUS Element Stent (N=768)
Peripheral vascular disease	8.8% (66/754)	9.1% (70/766)

Numbers are % (count/sample size) or Mean±SD (n) (min, max)
1: Reported as receiving medical treatment for the condition
Abbreviations: CAD=coronary artery disease; CI=confidence interval; CVA=cerebrovascular accident; ITT=intent-to-treat; LVEF=left ventricular ejection fraction; NA=not applicable; TIA=transient ischemic attack

As shown in **Table 13**, treatment groups had similar baseline lesion characteristics in the ITT population, as determined by core lab QCA. In both cohorts, RVD was approximately 2.65 mm, lesion length was approximately 12.73 mm, diameter stenosis was approximately 72%, and over 60% of treated lesions were type B2/C.

Table 13: Baseline Lesion Characteristics – By Lesion, ITT, All Target Lesions (N=1694) for All Patients (N=1530)

Lesion Characteristic	PROMUS Stent (N=841 Lesions, 762 Patients)	PROMUS Element Stent (N=853 Lesions, 768 Patients)
Quantitative Coronary Angiography Analyses		
Target lesion vessel		
LAD	42.1% (354/841)	41.9% (357/852)
LCx	26.0% (219/841)	26.1% (222/852)
RCA	31.9% (268/841)	32.0% (273/852)
LMCA	0.0% (0/841)	0.0% (0/852)
Lesion location		
Proximal	40.2% (338/841)	40.8% (348/852)
Mid	47.7% (401/841)	45.4% (387/852)
Distal	8.6% (72/841)	9.9% (84/852)
Ostial	3.6% (30/841)	3.9% (33/852)
Reference vessel diameter (mm)	2.63±0.49 (841) (1.52,4.55)	2.67±0.49 (852) (1.38,4.37)
Minimum lumen diameter (mm)	0.74±0.34 (841) (0.07,2.23)	0.75±0.35 (852) (0.05,1.95)
Diameter stenosis (%)	71.90±11.47 (841) (34.42,97.43)	71.81±11.46 (852) (37.86,98.29)
Lesion length (mm)	12.50±5.51(841) (3.20,44.69)	12.95±5.74 (852) (2.08,55.61)
Eccentric lesion	54.0% (454/841)	56.1% (477/851)
Bend	28.27±17.90(841) (0.00,105.00)	28.63±18.00(852) (0.00,115.00)
≥ 45%	16.9% (142/841)	17.4% (148/852)
≥ 90%	2.1% (18/841)	1.5% (13/852)
Thrombus, any	0.4% (3/841)	0.1% (1/852)
Tortuosity, any	7.4% (62/841)	8.5% (72/852)
Moderate	6.2% (52/841)	7.0% (60/852)

Table 13: Baseline Lesion Characteristics – By Lesion, ITT, All Target Lesions (N=1694) for All Patients (N=1530)

Lesion Characteristic	PROMUS Stent (N=841 Lesions, 762 Patients)	PROMUS Element Stent (N=853 Lesions, 768 Patients)
Severe	1.2% (10/841)	1.4% (12/852)
Calcification, any	28.1% (236/841)	27.9% (238/852)
Moderate	20.9% (176/841)	21.6% (184/852)
Severe	7.1% (60/841)	6.3% (54/852)
Ulcer	4.4% (37/841)	3.6% (31/852)
Aneurysm	1.3% (11/841)	1.6% (14/852)
Total occlusion	0.7% (6/841)	0.6% (5/852)
Branch vessel disease	7.4% (62/841)	9.2% (78/852)
Side branch stenosis	66.92±10.83(62) (55.00,99.00)	67.37±11.47(78) (55.00,100.00)
Modified ACC/AHA		
A	9.8% (82/841)	8.5% (72/852)
B1	26.8% (225/841)	26.2% (223/852)
B2	42.9% (361/841)	44.4% (378/852)
C	20.6% (173/841)	21.0% (179/852)
B2/C	63.5% (534/841)	65.4% (557/852)
Pre-Procedure TIMI Flow		
0	0.0% (0/841)	0.0% (0/852)
1	0.7% (6/841)	0.6% (5/852)
2	3.2% (27/841)	3.4% (29/852)
3	96.1% (808/841)	96.0% (818/852)
Site Reported Lesion Characteristics		
Lesion length (mm)	13.46±5.09 (839) (2.00,24.00)	14.24±5.29 (851) (1.00,24.00)
Reference vessel diameter (mm)	3.06±0.45 (839) (2.25,4.60)	3.09±0.45 (851) (2.00,4.24)
Diameter stenosis (%)	82.39±10.55 (841) (40.00,99.00)	82.26±10.30 (852) (50.00,99.00)

Numbers are % (count/sample size) or mean±SD (n) (min, max)
Abbreviation: ACC/AHA=American College of Cardiology/American Heart Association; CI=confidence interval; DS=diameter stenosis; ITT=intent-to-treat; LAD=left anterior descending; LCX=left circumflex; LMCA=left main coronary artery; MLD=minimum lumen diameter; QCA=quantitative coronary angiography; RCA=right coronary artery; TIMI=thrombolysis in myocardial infarction; Undef=undefined

A3. Safety and Effectiveness Results

The primary endpoint was met. The PROMUS Element stent was shown to be non-inferior to the PROMUS® stent with regard to the rate of 12-month TLF (**Table 14**). The two stents were similar with respect to post-procedure angiographic outcomes (**Table 15**) and the rates of all death, cardiac death, MI, revascularization, and stent thrombosis (**Table 16** and **Table 17**).

Table 14: PLATINUM Workhorse Primary Endpoint

Per Protocol Patients[1]	PROMUS Stent[2] (n=747)	PROMUS Element Stent (n=756)	Difference	One-sided 95% Farrington-Manning Upper Confidence Bound	Non-Inferiority Margin	*P* value[3]
12-Month TLF	2.9% (21/714)	3.4% (25/731)	0.5%	2.13%	3.5%	0.0013
Intent-to-Treat Patients	**PROMUS Stent[2] (n=762)**	**PROMUS Element Stent (n=768)**	**Difference**	**One-sided 95% Farrington-Manning Upper Confidence Bound**	**Non-Inferiority Margin**	***P* value[3]**
12-Month TLF	3.2% (23/727)	3.5% (26/742)	0.3%	2.01%	3.5%	0.0009

[1] Primary analysis for assessing hypothesis of non-inferiority and study success criterion. For per protocol analyses, only PLATINUM Workhorse trial patients who had the randomly assigned study stent implanted in the target coronary artery were included.
[2] Drug eluting stent Control
[3] *P* values are one-sided from the Farrington-Manning test and are based on the standard normal distribution.
12-Month TLF: the proportion of patients who experience a target lesion failure (TLF, defined as any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI,Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 15: PLATINUM Workhorse Post-Procedure Angiographic Results by Lesion

Angiographic Outcomes	PROMUS Stent[1] (N=841 Target Lesions, 762 Patients)	PROMUS Element Stent (N=853 Target Lesions, 768 Patients)
MLD (mm), In-stent	2.54±0.44(839)	2.57±0.42(846)
MLD (mm), Analysis Segment	2.16±0.47(840)	2.19±0.47(850)
Acute Gain (mm), In-stent	1.80±0.45(839)	1.81±0.43(846)
Acute Gain, Analysis Segment (mm)	1.42±0.47(840)	1.44±0.46(850)
% DS, In-stent	4.30±8.74(839)	4.27±9.09(846)
% DS, Analysis Segment	19.16±9.02(840)	18.82±8.63(850)

[1] DES Control
Numbers are mean±SD (n)
Abbreviations: DES=drug-eluting stent; DS=diameter stenosis; MLD=minimum lumen diameter.

Table 16: PLATINUM Workhorse Safety and Efficacy Results

	1-year (ITT Patients)	
	PROMUS Stent[1] (N=762)	**PROMUS Element Stent (N=768)**
EFFICACY		
TVR, Overall	2.9% (21/732)	2.7% (20/745)
TLR, Overall	1.9% (14/732)	1.9% (14/745)
TLR, PCI	1.6% (12/732)	1.3% (10/745)
TLR, CABG	0.3% (2/732)	0.5% (4/745)
Non-TLR, Overall	1.1% (8/732)	0.9% (7/745)
Non-TLR, PCI	1.1% (8/732)	0.8% (6/745)
Non-TLR, CABG	0.0% (0/732)	0.1% (1/745)
SAFETY		
Total Death	1.2% (9/732)	1.3% (10/745)
Cardiac Death or MI	2.5% (18/732)	2.0% (15/745)
Cardiac Death	0.7% (5/732)	0.9% (7/745)
MI	1.8% (13/732)	1.1% (8/745)
Q-wave MI	0.7% (5/732)	0.1% (1/745)
Non−Q-wave MI	1.2% (9/732)	0.9% (7/745)
ARC Stent Thrombosis		
Definite or Probable	0.4% (3/725)	0.4% (3/735)
Definite	0.4% (3/725)	0.4% (3/735)
Probable	0.0% (0/725)	0.0% (0/735)

Numbers are % (count/sample size)
[1] DES Control
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 17: PLATINUM Workhorse ARC Definite and Probable Stent Thrombosis

Intent-to-Treat Patients	PROMUS Stent[2] (N=762)	PROMUS Element Stent (N=768)
ARC Definite & Probable Stent Thrombosis [1]		
Cumulative through 1 year	0.4% (3/725)	0.4% (3/735)
Acute ST (≤24 hrs)	0.1% (1/762)	0.1% (1/768)
Subacute ST (>24 hrs and ≤30 days)	0.3% (2/762)	0.0% (0/766)
Late ST (>30 days and ≤12 months)	0.0% (0/760)	0.3% (2/764)

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

[1] Academic Research Consortium (ARC) stent thrombosis is defined as follows:

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   Any unexplained death within the first 30 days following stent implantation.
   Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

[2] DES Control

Numbers are % (count/sample size).

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Abbreviations: DES=drug-eluting stent; MI=myocardial infarction; ST=stent thrombosis

Observed Adverse Events

Observed adverse event experience comes from the PLATINUM Workhorse RCT. Major clinical events for this study are shown in **Table 18**.

Table 18. PLATINUM Workhorse, PLATINUM Small Vessel and PLATINUM QCA Major Clinical Events From Post-Procedure to 1-Year Follow-Up

	PLATINUM Workhorse	
	PROMUS Element Stent (n=768)	**PROMUS Stent[1] (n=762)**
In-Hospital All death, MI, TVR	0.9% (7/768)	1.2% (9/762)
All Death	0.1% (1/768)	0.0% (0/762)
Cardiac Death	0.1% (1/768)	0.0% (0/762)
Non-cardiac Death	0.0% (0/768)	0.0% (0/762)
MI	0.7% (5/768)	1.0% (8/762)
Q-Wave MI	0.0% (0/768)	0.3% (2/762)
Non-Q-Wave MI	0.7% (5/768)	0.8% (6/762)
Cardiac death or MI	0.8% (6/768)	1.0% (8/762)
TVR	0.1% (1/768)	0.7% (5/762)
TLR	0.1% (1/768)	0.7% (5/762)
Non-TLR	0.0% (0/768)	0.0% (0/762)
30-Day All death, MI, TVR	0.9% (7/766)	1.6% (12/761)
1-Year All death, MI, TVR	5.0% (37/745)	4.9% (36/732)
All Death	1.3% (10/745)	1.2% (9/732)
Cardiac Death	0.9% (7/745)	0.7% (5/732)
Non-cardiac Death	0.4% (3/745)	0.5% (4/732)
MI	1.1% (8/745)	1.8% (13/732)
Q-Wave MI	0.1% (1/745)	0.7% (5/732)
Non-Q-Wave MI	0.9% (7/745)	1.2% (9/732)
TVR	2.7% (20/745)	2.9% (21/732)
TLR	1.9% (14/745)	1.9% (14/732)
Non-TLR	0.9% (7/745)	1.1% (8/732)
In-Hospital ARC Stent Thrombosis		
Definite or Probable	0.1% (1/768)	0.1% (1/762)
Definite	0.1% (1/768)	0.1% (1/762)
Probable	0.0% (0/768)	0.0% (0/762)
1-Year ARC Stent Thrombosis		
Definite or Probable	0.4% (3/735)	0.4% (3/725)
Definite	0.4% (3/735)	0.4% (3/725)
Probable	0.0% (0/735)	0.0% (0/725)

[1] DES Control

Numbers are % (Count/Sample Size)

Abbreviations: ARC=Academic Research Consortium; DES=drug-eluting stent; MI=myocardial infarction; QCA=Quantitative Coronary Angiography; TLR=target lesion revascularization; TVR=target vessel revascularization.

Results in patients with and without diabetes

Patients with diabetes mellitus represent a high-risk group for adverse events following percutaneous coronary intervention. **Tables 19** and **20** show 1-year outcomes in patients with and without medically treated diabetes (defined as treatment with oral hypoglycemic agents or insulin at enrollment). While the PLATINUM WH study randomization was stratified for diabetic status, this trial was not adequately powered to study safety or effectiveness of the PROMUS Element stent versus the PROMUS® stent in patients with or without medically treated diabetes and was not designed to specifically support an approval for use in diabetic patients. These exploratory analyses suggest that in patients treated with the PROMUS Element stent, 1-year TLR rates were 3.7% in medically treated diabetic and 1.4% in non-diabetic patients.

Table 19: PLATINUM Workhorse Clinical Results in Patients with Medically Treated Diabetes

	1-year (ITT Patients)	
	PROMUS Stent[1] (N=191)	**PROMUS Element Stent (N=169)**
EFFICACY		
TVR, Overall	2.7% (5/186)	4.9% (8/163)
TLR, Overall	1.6% (3/186)	3.7% (6/163)
TLR, PCI	1.1% (2/186)	1.8% (3/163)
TLR, CABG	0.5% (1/186)	1.8% (3/163)
Non-TLR, Overall	1.1% (2/186)	1.2% (2/163)
Non-TLR, PCI	1.1% (2/186)	1.2% (2/163)
Non-TLR, CABG	0.0% (0/186)	0.0% (0/163)
TLF	2.7% (5/184)	4.3% (7/162)
SAFETY		
Total Death	1.6% (3/186)	1.2% (2/163)
Cardiac Death or MI	1.1% (2/186)	1.8% (3/163)
Cardiac Death	0.5% (1/186)	1.2% (2/163)
MI	0.5% (1/186)	0.6% (1/163)
Q-wave MI	0.0% (0/186)	0.0% (0/163)
Non-Q-wave MI	0.5% (1/186)	0.6% (1/163)
ARC Stent Thrombosis		
Definite or Probable	0.0% (0/184)	0.0% (0/160)
Definite	0.0% (0/184)	0.0% (0/160)
Probable	0.0% (0/184)	0.0% (0/160)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
[1] DES Control
Numbers are % (count/sample size)
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 20: PLATINUM Workhorse Clinical Results in Patients without Medically Treated Diabetes

	1-year (ITT Patients)	
	PROMUS Stent[1] (N=571)	PROMUS Element Stent (N=599)
EFFICACY		
TVR, Overall	2.9% (16/546)	2.1% (12/582)
TLR, Overall	2.0% (11/546)	1.4% (8/582)
TLR, PCI	1.8% (10/546)	1.2% (7/582)
TLR, CABG	0.2% (1/546)	0.2% (1/582)
Non-TLR, Overall	1.1% (6/546)	0.9% (5/582)
Non-TLR, PCI	1.1% (6/546)	0.7% (4/582)
Non-TLR, CABG	0.0% (0/546)	0.2% (1/582)
TLF	3.3% (18/543)	3.3% (19/580)
SAFETY		
Total Death	1.1% (6/546)	1.4% (8/582)
Cardiac Death or MI	2.9% (16/546)	2.1% (12/582)
Cardiac Death	0.7% (4/546)	0.9% (5/582)
MI	2.2% (12/546)	1.2% (7/582)
Q-wave MI	0.9% (5/546)	0.2% (1/582)
Non-Q-wave MI	1.5% (8/546)	1.0% (6/582)
ARC Stent Thrombosis		
Definite or Probable	0.6% (3/541)	0.5% (3/575)
Definite	0.6% (3/541)	0.5% (3/575)
Probable	0.0% (0/541)	0.0% (0/575)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
[1] DES Control
Numbers are % (count/sample size)
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

B. PLATINUM Small Vessel

B1. Clinical Study Design

Primary Objective: The objective of the study is to evaluate the safety and effectiveness of the PROMUS Element Everolimus-Eluting Coronary Stent System for the treatment of patients with a de novo lesion ≤28 mm in length (by visual estimate) in a native coronary artery ≥2.25 mm to <2.50 mm in diameter (by visual estimate).

Design: PLATINUM Small Vessel (SV) is a prospective, single-arm, multi-center sub-study of the PLATINUM Trial which was designed to evaluate the PROMUS Element Everolimus-Eluting Platinum Chromium Coronary Stent System in the treatment of *de novo* coronary lesions. The sub-study compares outcomes in patients treated with the 2.25 mm PROMUS Element stent

to a performance goal based outcomes in patients with one planned 2.25 mm TAXUS Express stent from the TAXUS V *De Novo* Trial. The primary endpoint was 12-month TLF, defined as any schemia-driven revascularization of the target lesion (TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death related to the target vessel.

Eligible patients were those ≥18 years old with LVEF ≥30% and with documented stable angina pectoris, silent ischemia, or unstable angina pectoris. *De novo* target lesions in a native coronary artery with diameter stenosis ≥50% and <100% with TIMI flow >1, RVD ≥2.25 mm to <2.50 mm (visual estimate), and lesion length ≤28 mm (visual estimate) were eligible. Patients were treated for a single target lesion and could also have 1 *de novo* native coronary artery lesion within a different epicardial vessel (non-target lesion) treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure. The non-target lesion had to be treated before the target lesion and the treatment had to be a clinical angiographic success (defined as visually assessed stenosis <50% [<30% for stents] with TIMI 3 flow without prolonged chest pain or ECG changes consistent with MI) before the patient could be enrolled. Patients were to have provided informed consent. A complete list of inclusion and exclusion criteria is included in **Section X – A1. Pivotal Clinical Study Design**.

After hospital discharge, enrolled patients are to undergo clinical follow-up at 30 days, 6 months, 12 months, 18 months, 2 years, and annually to 5 years post-index procedure. Starting with the 18-month visit, follow-up will be limited to the safety analysis set, which is composed of all study patients who received a PROMUS Element stent. Follow-up is complete through 1 year, the timing at which the primary endpoint for the trial was assessed, with additional follow-up ongoing. Regarding antiplatelet therapy, the protocol mandated compliance with ACC/AHA/SCAI Guidelines for PCI.[1]

An angiographic core lab was utilized for analysis of angiography data. A Clinical Events Committee (CEC) served as a multidisciplinary expert group responsible for the independent and ongoing adjudication of prespecified clinical events, including all reported deaths, MIs, TVRs, and STs, as defined by the clinical protocol. A Data Monitoring Committee (DMC) of independent experts in cardiology, cardiovascular interventional therapy, and biostatistics worked to ensure patient safety by evaluating accumulating data from the PLATINUM Clinical Program.

Baseline, procedural, and follow-up data were summarized using descriptive statistics for continuous variables and frequency tables or proportions for discrete variables. Clinical and success/failure event rates are presented below as proportions with 95% confidence intervals. Continuous data are summarized by means, standard deviations, sample sizes, minimums, and maximums; 95% confidence intervals of the means are provided. All analyses of primary and additional endpoints were based on patients with sufficient follow-up. Endpoints were analyzed using 2 populations: ITT (N=94) and per-protocol (N=89, includes only patients who received a study stent).

The rate of the primary endpoint, TLF at 12 months, was compared to a predefined performance goal (PG) of 21.1% based on historical TAXUS Express results. The PG equals the historical TAXUS Express Small Vessel 12-month TLF rate of 18.6% plus a 2.5% delta. The historical

TAXUS Express Small Vessel rate is the rate of 12-month TLF for patients in the TAXUS V *De Novo* Trial with one planned TAXUS Express 2.25 mm stent, adjusted for oculostenotic reflex due to protocol mandated angiographic follow-up, which was not required in the PLATINUM trial. A one-group exact binomial test was used to test the hypothesis that the primary endpoint rate in the PROMUS Element cohort is less than the PG.

B2. Accountability of PMA Cohort

A total of 94 patients were enrolled at 23 clinical sites in Australia, Belgium, France, Japan, New Zealand, and the United States from February 9, 2009 to December 10, 2009. Of the 94 patients included in the intent-to-treat analysis set, a total of 89 patients were evaluable for the 12-month primary endpoint. Patient disposition for the ITT analysis set is shown in **Table 21**.

Table 21: Patient Disposition for PLATINUM SV Study, ITT, All Patients (N=94)

Category	PROMUS Element Stent
Intent-to-Treat Analysis Set	94
Death ≤395 days, no 12-month clinical follow-up performed	4
Eligible for 12-month clinical follow-up[a]	90
12-month clinical follow-up performed[b]	95.6% (86/90)
Office visit	78
Telephone contact	8
No 12-month clinical follow-up performed	4
Prematurely discontinued	1
Death > 395 days	0
Withdrew consent	1
Lost to follow-up	0
Adverse event	0
Investigator discretion	0
Transplant or removal of target organ	0
Other	0
Missed 12-month visit	3
With later follow-up visit performed	0
No later follow-up visit performed	3
12-month clinical follow-up or death[c]	95.7% (90/94)
12-month clinical follow-up patient accountability[d]	91.5% (86/94)

Numbers are counts of patients or % (count/sample size).
a: Patients who died prior to completion of follow-up window and prior to completing a 12-month clinical follow-up visit are considered censored and are excluded from calculation of proportion of patients who completed clinical follow-up visit.
b: Based on patients eligible for 12-month clinical follow-up
c: Includes patients who have died in both the numerator and the denominator; based on the ITT analysis set
d: All patients with 12-month follow-up out of all ITT patients
Abbreviations: ITT=intent-to-treat; SV=small vessel

B3. Study Population Demographics and Baseline Parameters

Table 22 presents baseline demographic and clinical characteristics for the ITT analysis set (N=94). Average age was 64.3±11.0. Approximately 72% of patients were male, and 43% of patients were medically treated diabetics.

Table 22: Baseline Demographics and Clinical Characteristics, ITT Analysis Set (N=94)

Parameter	PROMUS Element Stent (N=94)
Male	72.3% (68/94)
Age (years)	64.33±11.03 (94) (37.00, 87.00)
General Medical History	
Smoking, ever	62.8% (59/94)
Current	17.0% (16/94)
Previous	45.7% (43/94)
Diabetes (medically treated)	42.6% (40/94)
Insulin	11.7% (11/94)
Oral medications (no insulin)	30.9% (29/94)
Diabetes treated with diet only	4.3% (4/94)
Hyperlipidemia (medically treated)	81.9% (77/94)
Hypertension (medically treated)	79.8% (75/94)
History of bleeding disorder	1.1% (1/94)
Gastrointestinal	1.1% (1/94)
Hematologic dyscrasia	0.0% (0/94)
Cardiac History	
Angina, stable	53.2% (50/94)
Angina, unstable	24.5% (23/94)
Angina, none	22.3% (21/94)
Silent ischemia	22.8% (21/92)
Family history of coronary artery disease	62.0% (57/92)
Previous myocardial infarction	29.8% (28/94)
History of congestive heart failure	9.7% (9/93)
Previous percutaneous coronary intervention	43.6% (41/94)
Previous coronary artery bypass graft	13.8% (13/94)
History of arrhythmia	12.9% (12/93)
Left ventricular ejection fraction (%)	58.07±10.00 (94) (34.00, 88.00)
Not measured or not known	0.0% (0/94)
History of multivessel disease	46.8% (44/94)
History of left main disease	3.2% (3/94)
Neurologic, Renal, and Peripheral History	
History of TIA or CVA	7.4% (7/94)
Transient ischemic attack (TIA)	5.3% (5/94)

Table 22: Baseline Demographics and Clinical Characteristics, ITT Analysis Set (N=94)

Parameter	PROMUS Element Stent (N=94)
Cerebrovascular accident (CVA)	3.2% (3/94)
History of renal disease	2.1% (2/94)
History of peripheral vascular disease	13.8% (13/94)
Numbers are presented as mean±standard deviation (n) (minimum, maximum) or % (count/sample size). Abbreviations: CAD=coronary artery disease; CI=confidence interval; CVA=cerebrovascular accident; ITT=intent-to-treat; LVEF=left ventricular ejection fraction; NA=not applicable; TIA=transient ischemic attack	

Table 23 presents baseline lesion characteristics for the ITT population as determined by core lab QCA. Mean reference vessel diameter (RVD) was 2.04±0.26 mm. Average lesion length was 14.15±7.03 mm. Diameter stenosis was approximately 75%, and approximately 69% of treated lesions were type B2/C.

Table 23: Baseline Lesion Characteristics, by Lesion, ITT Analysis Set (N=94)

Parameter	PROMUS Element Stent (N=94)
Quantitative Coronary Angiography Analyses	
Target lesion vessel	
Left anterior descending artery	34.0% (32/94)
Left circumflex artery	43.6% (41/94)
Right coronary artery	22.3% (21/94)
Left main coronary artery	0.0% (0/94)
Lesion location	
Proximal	42.6% (40/94)
Mid	39.4% (37/94)
Distal	16.0% (15/94)
Ostial	2.1% (2/94)
Reference vessel diameter (mm)	2.04±0.26(94) (1.59,2.65)
Minimum lumen diameter (mm)	0.51±0.21(94) (0.10,1.12)
Percent diameter stenosis	75.10±9.50(94) (50.33,94.80)
Lesion length (mm)	14.15±7.03(94) (3.92,39.48)
Eccentric lesion	70.2% (66/94)
Bend	29.52±19.33(94) (5.00,100.00)
Thrombus	1.1% (1/94)
Tortuosity, any	5.3% (5/94)
Moderate	5.3% (5/94)
Severe	0.0% (0/94)
Calcification, any	24.5% (23/94)

Table 23: Baseline Lesion Characteristics, by Lesion, ITT Analysis Set (N=94)

Parameter	PROMUS Element Stent (N=94)
Moderate	20.2% (19/94)
Severe	4.3% (4/94)
Ulcer	0.0% (0/94)
Aneurysm	1.1% (1/94)
Total occlusion	0.0% (0/94)
Branch vessel disease	6.4% (6/94)
Side branch stenosis	61.67±5.16(6) (55.00,70.00)
Lesion type (modified ACC/AHA)	
A	8.5% (8/94)
B1	22.3% (21/94)
B2	43.6% (41/94)
C	25.5% (24/94)
Preprocedure TIMI flow	
0	0.0% (0/94)
1	0.0% (0/94)
2	6.4% (6/94)
3	93.6% (88/94)
Site Reported Lesion Characteristics	
Lesion length (mm)	14.32±6.81(94) (5.00,28.00)
Reference vessel diameter (mm)	2.27±0.05(94) (2.25,2.45)
Diameter stenosis (%)	84.91±9.25(94) (65.00,99.00)

Numbers are presented as mean±standard deviation (n) (minimum, maximum) or % (count/sample size).
Abbreviation: ACC/AHA=American College of Cardiology/American Heart Association; ITT=intent-to-treat; TIMI=thrombolysis in myocardial infarction

B4. Safety and Effectiveness Results

The primary endpoint was met (**Table 24**). The rate of 12-Month TLF was shown to be significantly less than the performance goal. Post-procedure angiographic outcomes are shown in **Table 25** and rates for all death, cardiac death, MI, revascularization, and stent thrombosis are shown in **Table 26** and **Table 27**.

Table 24: PLATINUM Small Vessel Primary Endpoint

Per Protocol Patients[1]	PROMUS Element Stent (n=89)	[95% CI]	One-sided 95% Clopper-Pearson Upper Confidence Bound	Performance Goal	*P* value[2]
12-Month TLF	2.4% (2/84)	[0.3%, 8.3%]	7.31%	21.1%	<0.0001

Intent-to-Treat Patients	PROMUS Element Stent (n=94)	[95% CI]	One-sided 95% Clopper-Pearson Upper Confidence Bound	Performance Goal	*P* value[2]
12-Month TLF	5.6% (5/89)	[1.8%, 12.6%]	11.45%	21.1%	<0.0001

[1] Primary analysis for comparing to the performance goal and study success criterion.
[2] *P* values are one-sided from the exact binomial test.
12-Month TLF: the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non-Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 25: PLATINUM Small Vessel Post-Procedure Angiographic Results

Angiographic Outcomes	PROMUS Element Stent (N=94 Patients)
MLD (mm), In-stent	1.98±0.19(91)
MLD (mm), Analysis Segment	1.64±0.32(94)
Acute Gain (mm), In-stent	1.47±0.27(91)
Acute Gain, Analysis Segment (mm)	1.13±0.35(94)
% DS, In-stent	3.95±10.95(91)
% DS, Analysis Segment	21.29±10.17(94)
Abbreviations: DS=diameter stenosis; MLD=minimum lumen diameter.	

Table 26: PLATINUM Small Vessel Clinical Results

	1-year (ITT Patients)
	PROMUS Element Stent (N=94)
EFFICACY	
TVR, Overall	3.3% (3/90)
TLR, Overall	2.2% (2/90)
TLR, PCI	2.2% (2/90)
TLR, CABG	0.0% (0/90)
Non-TLR, Overall	1.1% (1/90)
Non-TLR, PCI	1.1% (1/90)
Non-TLR, CABG	0.0% (0/90)
SAFETY	
Total Death	4.4% (4/90)
Cardiac Death or MI	3.3% (3/90)
Cardiac Death	3.3% (3/90)
MI	0.0% (0/90)

Table 26: PLATINUM Small Vessel Clinical Results

	1-year (ITT Patients)
	PROMUS Element Stent (N=94)
Q-wave MI	0.0% (0/90)
Non-Q-wave MI	0.0% (0/90)
ARC Stent Thrombosis	
Definite or Probable	0.0% (0/86)
Definite	0.0% (0/86)
Probable	0.0% (0/86)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (count/sample size)
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 27: PLATINUM Small Vessel ARC Definite and Probable Stent Thrombosis

Intent-to-Treat Patients	PROMUS Element Stent (N=94)
ARC Definite & Probable Stent Thrombosis [1]	
Cumulative through 1 year	0.0% (0/86)
Acute ST (≤24 hrs)	0.0% (0/94)
Subacute ST(>24 hrs and ≤30 days)	0.0% (0/94)
Late ST (>30 days and ≤12 months)	0.0% (0/94)

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).
[1] Academic Research Consortium (ARC) stent thrombosis is defined as follows:

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   Any unexplained death within the first 30 days following stent implantation.
   Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

Numbers are % (Count/Sample Size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Abbreviations: MI=myocardial infarction; ST=stent thrombosis

Observed Adverse Events:

Observed adverse event experience comes from the PLATINUM Small Vessel Sub-study. Major clinical events for this study are shown in **Table 28**.

Table 28. PLATINUM Small Vessel Major Clinical Events From Post-Procedure to 1-Year Follow-Up	
	PLATINUM Small Vessel
	PROMUS Element Stent (n=94)
In-Hospital All death, MI, TVR	0.0% (0/94)
All Death	0.0% (0/94)
Cardiac Death	0.0% (0/94)
Non-cardiac Death	0.0% (0/94)
MI	0.0% (0/94)
Q-Wave MI	0.0% (0/94)
Non-Q-Wave MI	0.0% (0/94)
Cardiac death or MI	0.0% (0/94)
TVR	0.0% (0/94)
TLR	0.0% (0/94)
Non-TLR	0.0% (0/94)
30-Day All death, MI, TVR	0.0% (0/94)
1-Year All death, MI, TVR	7.8% (7/90)
All Death	4.4% (4/90)
Cardiac Death	3.3% (3/90)
Non-cardiac Death	1.1% (1/90)
MI	0.0% (0/90)
Q-Wave MI	0.0% (0/90)
Non-Q-Wave MI	0.0% (0/90)
TVR	3.3% (3/90)
TLR	2.2% (2/90)
Non-TLR	1.1% (1/90)
In-Hospital ARC Stent Thrombosis	
Definite or Probable	0.0% (0/94)
Definite	0.0% (0/94)
Probable	0.0% (0/94)
1-Year ARC Stent Thrombosis	
Definite or Probable	0.0% (0/86)
Definite	0.0% (0/86)
Probable	0.0% (0/86)

[1] DES Control
Numbers are % (Count/Sample Size)
Abbreviations: ARC=Academic Research Consortium; DES=drug-eluting stent; MI=myocardial infarction; QCA=Quantitative Coronary Angiography; TLR=target lesion revascularization; TVR=target vessel revascularization.

C. PLATINUM QCA

Primary Objective: The primary objective of the PLATINUM QCA Trial was to evaluate the clinical, angiographic, and IVUS outcomes of the PROMUS Element Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of de novo atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of 2.25 mm to 4.25 mm in diameter (by visual estimate).

Design: PLATINUM QCA is a prospective, single-arm, multi-center, observational study designed to evaluate clinical, angiographic and IVUS outcomes in *de novo* atherosclerotic lesions treated with the PROMUS Element Everolimus-Eluting Platinum Chromium Coronary Stent System. This study was conducted OUS (Outside-of-US) in Australia, Malaysia, New Zealand and Singapore, and is complete. The primary endpoint was the 30-day composite rate of cardiac death, MI (Q-wave and non−Q-wave), TLR, and ST. Efficacy endpoints included in-stent late loss at 9 months (determined by QCA) in patients with WH target lesions (visual RVD ≥2.5 mm and ≤4.25 mm and visual lesion length ≤24 mm) and post-procedure incomplete apposition (determined by intravascular ultrasound [IVUS]).

Eligible patients were ≥18 years old with left ventricular ejection fraction (LVEF) ≥30% and documented stable angina pectoris, silent ischemia, or unstable angina pectoris. *De novo* target lesions in a native coronary artery with diameter stenosis ≥50% and <100% with TIMI flow >1, RVD ≥2.25 mm to ≤4.25 mm (visual estimate), and lesion length ≤34 mm (visual estimate) were eligible. Patients were treated for a single target lesion and could also have 1 *de novo* native coronary artery lesion within a different epicardial vessel (non-target lesion) treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure. The non-target lesion had to be treated before the target lesion and the treatment had to be a clinical angiographic success (defined as visually assessed stenosis <50% [<30% for stents] with TIMI 3 flow without prolonged chest pain or ECG changes consistent with MI) before the patient could be enrolled. Patients were to have provided written informed consent.

After hospital discharge, enrolled patients were to undergo clinical follow-up at 30 days, 9 months, and 1 year post-index procedure. Angiography and IVUS were required at 9 months. Regarding antiplatelet therapy, the protocol mandated compliance with ACC/AHA/SCAI Guidelines for PCI.[1]

Angiographic and IVUS core labs were utilized for data analysis. A Clinical Events Committee (CEC) served as a multidisciplinary expert group responsible for the independent and ongoing adjudication of prespecified clinical events, including all reported deaths, MIs, TVRs, and STs, as defined by the clinical protocol. A Data Monitoring Committee (DMC) of independent experts in cardiology, cardiovascular interventional therapy, and biostatistics worked to ensure patient safety by evaluating accumulating data from the PLATINUM Clinical Program.

No formal statistical testing was performed for the primary endpoint in this single arm observational trial. The efficacy endpoint of 9-month in-stent late loss in WH target lesions was compared to a predefined PG of 0.44 mm based on historical TAXUS Express stent results and

the data were compared using a one group *t*-test. For the efficacy endpoint of post-procedure incomplete apposition, the PG of 34.4% was based on historical PROMUS® (Xience V) post-procedure incomplete apposition data from the SPIRIT III study and the data were compared using a one-group exact test. Baseline data were summarized using descriptive statistics for continuous variables and frequency tables/proportions for discrete variables. Clinical and success/failure event rates are presented below as proportions with 95% confidence intervals, and continuous data are summarized by means, standard deviations, sample sizes, minimums, and maximums; 95% confidence intervals of the means are provided.

C1. Accountability of PMA Cohort

A total of 100 patients were enrolled from March 10, 2009 through July 22, 2009 at 14 sites in the Asia Pacific region. Because all patients received a PROMUS Element stent, the ITT and per protocol analysis sets were identical. All 100 patients were evaluable for the 30-day primary endpoint. At 9 months post procedure, 88 patients underwent angiography and 83 underwent IVUS.

C2. Study Population Demographics and Baseline Parameters

Demographics: Average age was 61.8±9.9. 77% of patients were male, and 19% of patients had medically treated diabetes.

Baseline lesion characteristics: Reference vessel diameter was 2.72±0.53 mm with baseline lesion length 15.40±7.03 mm. Percent diameter stenosis was 74.09±10.93 and 67% of treated lesions were type B2/C.

C3. Safety and Effectiveness Results

The primary endpoint, 30-day composite rate of cardiac death, MI, TLR, and ARC definite/probable ST, was 1.0% (1/100) **(Table 29)**. Both efficacy endpoints were met **(Tables 30 and 31)**. The PROMUS Element in-stent late loss of 0.17±0.25 mm (n=73) in WH lesions at 9 months was significantly less than PG of 0.44 mm ($P<0.0001$). Post-procedure incomplete apposition with PROMUS Element was 5.7% (5/88), significantly less than the PG of 34.4% ($P<0.0001$).

Table 29. PLATINUM QCA Primary Endpoint

Per Protocol Patients	PROMUS Element Stent (N=100)
Cardiac Death, MI, TLR, ARC Stent Thrombosis (definite and probable) through 30 days	1.0% (1/100)
Cardiac Death	0.0% (0/100)
MI	0.0% (0/100)
Q-wave MI	0.0% (0/100)
Non-Q-wave MI	0.0% (0/100)

Table 29. PLATINUM QCA Primary Endpoint	
TLR	1.0% (1/100)
ARC ST (definite and probable)	1.0% (1/100)
Intent-to-Treat Patients	**PROMUS Element Stent (N=100)**
Cardiac Death, MI, TLR, ARC Stent Thrombosis (definite and probable) through 30 days	1.0% (1/100)
Cardiac Death	0.0% (0/100)
MI	0.0% (0/100)
Q-wave MI	0.0% (0/100)
Non-Q-wave MI	0.0% (0/100)
TLR	1.0% (1/100)
ARC ST (definite and probable)	1.0% (1/100)
Numbers are % (count/sample size) Abbreviations: ARC=Academic Research Consortium; MI=myocardial infarction; ST=stent thrombosis; TLR=target lesion revascularization	

Table 30: PLATINUM QCA Efficacy Endpoint: 9-Month In-stent Late Loss in Workhorse Patients

Intent-to-treat Workhorse Patients	PROMUS Element Stent (N=85)	[95% CI]	One-sided 95% upper confidence bound	Performance Goal	*P* value[1]
9-Month In-Stent Late Loss, mm	0.17±0.25 (73) (-0.41, 0.87)	[0.12, 0.23]	0.22	0.44	<0.0001

[1] *P* value is from the Student t-test. No adjustments to p-values were made for multiple comparisons.

Table 31: PLATINUM QCA Efficacy Endpoint: Post-procedure Incomplete Apposition

Intent-to-treat Patients	PROMUS Element Stent (N=100)	[95% CI]	One-sided 95% Clopper-Pearson upper confidence bound	Performance Goal	*P* value[1]
Post-procedure Incomplete Apposition	5.7% (5/88)	[1.9%, 12.8%]	11.6%	34.4%	<0.0001

[1] *P* value is from the exact binomial test. No adjustments to p-values were made for multiple comparisons.

Table 32: PLATINUM QCA Clinical Results

	1-year (ITT Patients)
	PROMUS Element Stent (N=100)
EFFICACY	
TVR, Overall	1.0% (1/100)
TLR, Overall	1.0% (1/100)
TLR, PCI	1.0% (1/100)
TLR, CABG	0.0% (0/100)
Non-TLR, Overall	1.0% (1/100)
Non-TLR, PCI	1.0% (1/100)
Non-TLR, CABG	0.0% (0/100)
SAFETY	
Total Death	0.0% (0/100)
Cardiac Death or MI	0.0% (0/100)
Cardiac Death	0.0% (0/100)
MI	0.0% (0/100)
Q-wave MI	0.0% (0/100)
Non–Q-wave MI	0.0% (0/100)
ARC Stent Thrombosis	
Definite or Probable	1.0% (1/100)
Definite	1.0% (1/100)
Probable	0.0% (0/100)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (count/sample size)
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 33: PLATINUM QCA Angiographic and IVUS Results

Angiographic Outcomes[1]	**PROMUS Element Stent (N=100)**
Minimum Lumen Diameter (mm), In-stent	
Post-Procedure	2.64±0.46(88)
9-Month	2.44±0.49(88)
Minimum Lumen Diameter (mm), Analysis Segment	
Post-Procedure	2.27±0.52(88)
9-Month	2.20±0.49(88)
Acute Gain (mm), In-stent	1.93±0.47(88)
Acute Gain, Analysis Segment (mm)	1.56±0.51(88)
% Diameter Stenosis, In-stent	

Table 33: PLATINUM QCA Angiographic and IVUS Results

Angiographic Outcomes[1]	PROMUS Element Stent (N=100)
Post-Procedure	3.58±7.98(88)
9-Month	10.00±11.59(88)
% Diameter Stenosis, Analysis Segment	
Post-Procedure	17.99±7.88(88)
9-Month	19.66±8.95(88)
Late Loss, In-stent (mm)	0.20±0.28(88)
Late Loss, Analysis Segment (mm)	0.07±0.27(88)
Binary Restenosis	
In-stent Restenosis	1.1% (1/88)
Analysis Segment Restenosis	1.1% (1/88)
IVUS Outcomes	
Neointimal Volume (mm^3) (9 months)	12.73±11.74(73)
% In-stent Net Volume Obstruction (9 months)	7.24±6.22(73)
Incomplete Apposition	
Late (9 months)	0.0% (0/69)
Late Acquired	0.0% (0/69)

[1] Includes all patients with paired lesion data.
[2] Secondary endpoint of in-stent late loss (0.17±0.25 mm) is based on patients with workhorse lesions (n=73). Table 11.0-T5 includes all patients with QCA at 9 months (n=88).
Numbers are mean±std (n) or % (Count/Sample Size).

Table 34: PLATINUM QCA ARC Definite and Probable Stent Thrombosis

Intent-to-Treat Patients	PROMUS Element Stent (N=100)
ARC Definite & Probable Stent Thrombosis [1]	
Cumulative through 1 year	1.0% (1/100)
Acute ST (≤24 hrs)	1.0% (1/100)
Subacute ST (>24 hrs and ≤30 days)	0.0% (0/100)
Late ST (>30 days and ≤12 months)	0.0% (0/100)

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).
[1] Academic Research Consortium (ARC) stent thrombosis is defined as follows:

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   Any unexplained death within the first 30 days following stent implantation.
   Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

Numbers are % (Count/Sample Size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

C. Longitudinal Stent Deformation

It has recently been reported that crossing a newly deployed PROMUS Element stent with a second device, such as a balloon catheter, stent system or IVUS catheter, can lead to the second device becoming caught on the PROMUS Element stent. In this situation, if the second device is advanced or retracted, longitudinal stent deformation (i.e., longitudinal compression or elongation) of the PROMUS Element stent may occur, resulting in the need for additional treatment including repeat dilatation of the PROMUS Element, placement of a second stent, and/or surgical intervention.

Following the publication of three cases of longitudinal compression of a newly deployed DES (one of which was a PROMUS Element stent)[2] Boston Scientific reviewed: (1) the PERSEUS trial (ION Stent) and PLATINUM trial (PROMUS Element Stent); and (2) all worldwide complaints received concerning ION and non-US complaints concerning PROMUS Element and Omega (bare metal stent) stent systems, all of which use the same PtCr stent platform.

Although the rate of longitudinal stent deformation is unknown, currently available information suggests that it is a rare adverse event. No cases of longitudinal stent deformation were observed in the PERSEUS trial (ION Stent) or the PLATINUM trial (PROMUS Element Stent). Based on the evaluation of the worldwide complaints concerning the Element platform, as of 31 October, 2011, there were 136 of longitudinal stent deformation events per 829,372 units sold. Of a total of 136 patients in whom longitudinal stent deformation was reported, additional stents were implanted in 55 patients, and 4 patients underwent surgery. An analysis of the complaint reports suggests that coronary artery calcification, vessel tortuosity, and stent mal-apposition in conjunction with crossing a newly deployed stent with an ancillary device may be associated with an increased risk of longitudinal stent deformation.

PROMUS Element was engineered to be a flexible, conformable stent. Characterization testing conducted by BSC indicates that some design features intended to produce these performance attributes may be associated with a reduction in longitudinal strength and contribute to the occurrence of longitudinal stent deformation. Although the majority of cases appear to occur following contact with an ancillary device, the definitive cause of longitudinal stent deformation remains uncertain.

A precaution including this information has been included in the Directions for Use for the PROMUS Element Stent. Additional information will be gathered through Medical Device Reporting and through the condition of approval study (see Section XIII below).

D. PLATINUM Clinical Trial Program - Sex/Gender Analyses

To evaluate for possible sex-based differences in outcome of treatment with the ION Stent when used in small vessels, sex/gender-specific analyses were performed retrospectively on safety and effectiveness endpoints. The results suggest that the general conclusions of the overall study regarding both safety and effectiveness can be generalized for males and females.

PLATINUM Workhorse (WH) Trial:

PLATINUM WH data were evaluated retrospectively for possible gender-based differences in clinical outcomes, as well as for any interaction between treatment and gender. PLATINUM WH was not designed or powered to study safety or effectiveness of the PROMUS Element stent versus the PROMUS stent in gender-specific subgroups, so these analyses were performed post hoc and are considered hypothesis-generating.

In the PLATINUM WH ITT population, of the 768 patients randomized to PROMUS Element, 550 patients were male (71.6%) and 218 patients were female (28.4%). The proportions in the PROMUS group were similar (71.1% males, 28.9% females).

In the United States, an estimated 17,600,000 adults age 20 and older (9.1% of men and 7.0% of women) suffer from coronary artery disease (CAD)[3]. However, it is estimated that only 36% of annual PCIs are performed in women. In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology,[4] which may lead to under-diagnosis and under-referral of female patients with CAD. Once diagnosed and treated, poorer revascularization outcomes have been reported in women due to smaller coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men.

In patients treated with the PROMUS Element stent, the 12-month rate of TLF was 3.4% in males and 3.8% in females. In patients treated with the PROMUS stent, the 12-month rate of TLF was 3.1% in males and 3.4% in females **(Table 35).**

This *post hoc* analysis shows similar treatment effect between genders for the primary endpoint of 12-month TLF. This suggests that the overall conclusions of the trial regarding both safety and effectiveness of the PROMUS Element stent can be generalized to males and females.

Table 35. PLATINUM Workhorse Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=1530)

12-month TLF	PROMUS Stent (N=762)	PROMUS Element Stent (N=768)	Difference
Female (N=438)	**(N=220)**	**(N=218)**	
	3.4% (7/208)	3.8% (8/213)	0.4%
Male (N=1092)	**(N=542)**	**(N=550)**	
	3.1% (16/519)	3.4% (18/529)	0.3%

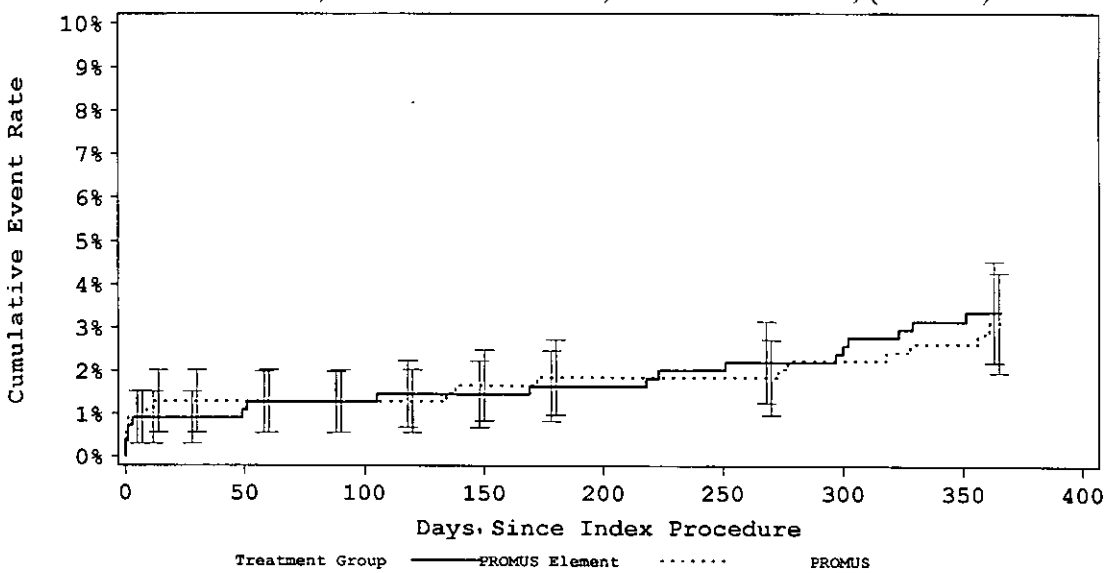
Table 35. PLATINUM Workhorse Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=1530)
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (Count/Sample Size) 12-Month TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 36 shows PLATINUM WH 12-month clinical results for PROMUS Element male and female patients. Outcomes were similar in male and female patients.

Table 36. PLATINUM Workhorse 12-Month Clinical Endpoints by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=768)		
	PROMUS Element Stent Male Patients (N=550)	**PROMUS Element Stent Female Patients (N=218)**
EFFICACY		
TVR, Overall	2.8% (15/532)	2.3% (5/213)
TLR, Overall	1.7% (9/532)	2.3% (5/213)
TLR, PCI	1.3% (7/532)	1.4% (3/213)
TLR, CABG	0.4% (2/532)	0.9% (2/213)
Non-TLR, Overall	1.3% (7/532)	0.0% (0/213)
Non-TLR, PCI	1.1% (6/532)	0.0% (0/213)
Non-TLR, CABG	0.2% (1/532)	0.0% (0/213)
TLF	3.4% (18/529)	3.8% (8/213)
SAFETY		
Total Death	1.7% (9/532)	0.5% (1/213)
Cardiac Death or MI	2.3% (12/532)	1.4% (3/213)
Cardiac Death	1.1% (6/532)	0.5% (1/213)
MI	1.1% (6/532)	0.9% (2/213)
Q-wave MI	0.2% (1/532)	0.0% (0/213)
Non-Q-wave MI	0.9% (5/532)	0.9% (2/213)
ARC Stent Thrombosis		
Definite or Probable	0.6% (3/524)	0.0% (0/211)
Definite	0.6% (3/524)	0.0% (0/211)
Probable	0.0% (0/524)	0.0% (0/211)
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (Count/Sample Size) Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass grafting; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization.		

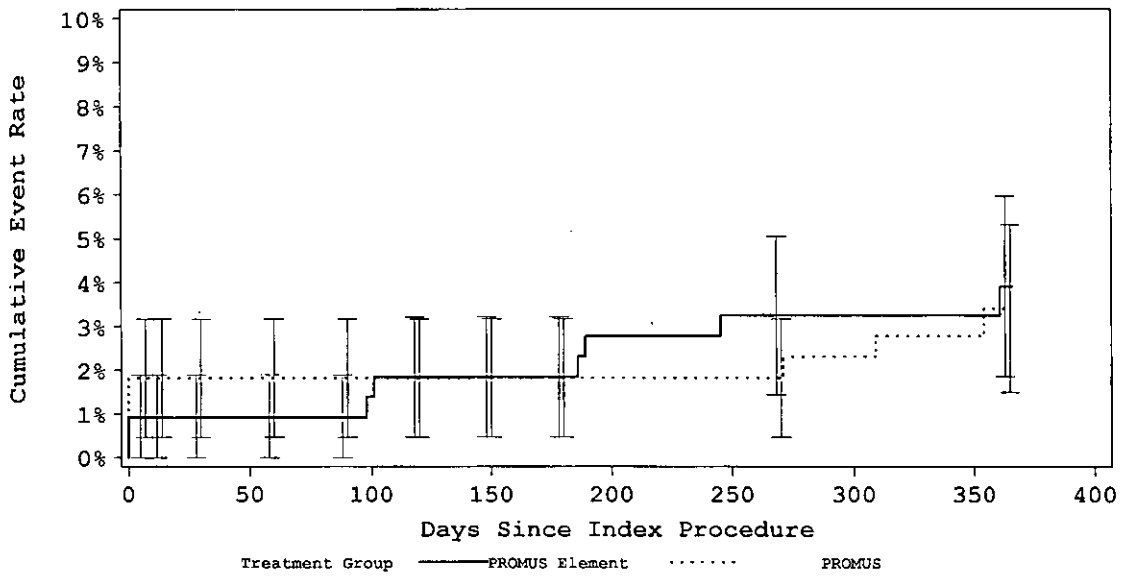
Figures 4 and 5 show the cumulative rate of TLF through 12-months for males and females, respectively. This *post hoc* analysis shows that there were similar TLF rates for PROMUS Element and PROMUS groups for males and females at all follow-up time-points (30 days, 6 months, and 12 months).

Figure 4. PLATINUM Workhorse Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate ± 1.5 SE, All Male Patients, (N=1092)



	Event Rate	Event Free
PROMUS Element	3.4%	96.6%
PROMUS DES Control	3.1%	96.9%

Figure 5. PLATINUM Workhorse Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate ± 1.5 SE, All Female Patients (N=438)



	Event Rate	Event Free
PROMUS Element	3.9%	96.1%
PROMUS DES Control	3.4%	96.6%

PLATINUM Small Vessel Trial:

In the PLATINUM SV ITT population, of the 94 patients enrolled, 68 patients were male (72.3%) and 26 patients were female (27.7%). In patients treated with the PROMUS Element stent, the 12-Month rate of TLF was 7.9% in males and 0% in females (**Table 36**). Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 36. PLATINUM Small Vessel Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=94)

	PROMUS Element Stent Male Patients (N=68)	PROMUS Element Stent Female Patients (N=26)	Difference
12-Month TLF	7.9% (5/63)	0.0% (0/26)	7.9%

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (Count/Sample Size)
12-Month TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 37 shows PLATINUM SV 12-month clinical results for male and female patients. There were no events through 12 months in the small population of female patients.

Table 37. PLATINUM Small Vessel 12-Month Clinical Endpoints by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=94)		
	PROMUS Element Stent Male Patients (N=68)	**PROMUS Element Stent Female Patients (N=26)**
EFFICACY		
TVR, Overall	4.7% (3/64)	0.0% (0/26)
TLR, Overall	3.1% (2/64)	0.0% (0/26)
TLR, PCI	3.1% (2/64)	0.0% (0/26)
TLR, CABG	0.0% (0/64)	0.0% (0/26)
Non-TLR, Overall	1.6% (1/64)	0.0% (0/26)
Non-TLR, PCI	1.6% (1/64)	0.0% (0/26)
Non-TLR, CABG	0.0% (0/64)	0.0% (0/26)
TLF	7.9% (5/63)	0.0% (0/26)
SAFETY		
Total Death	6.3% (4/64)	0.0% (0/26)
Cardiac Death or MI	4.7% (3/64)	0.0% (0/26)
Cardiac Death	4.7% (3/64)	0.0% (0/26)
MI	0.0% (0/64)	0.0% (0/26)
Q-wave MI	0.0% (0/64)	0.0% (0/26)
Non-Q-wave MI	0.0% (0/64)	0.0% (0/26)
ARC Stent Thrombosis		
Definite or Probable	0.0% (0/60)	0.0% (0/26)
Definite	0.0% (0/60)	0.0% (0/26)
Probable	0.0% (0/60)	0.0% (0/26)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (Count/Sample Size)
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass grafting; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization.

PLATINUM Quantitative Coronary Angiography (QCA) Trial:

In the PLATINUM QCA ITT population, of the 100 patients enrolled, 77 patients were male (77.0%) and 23 patients were female (23.0%). In patients treated with the PROMUS Element stent, the 12-Month rate of TLF was 0% in males and 4.3% in females (**Table 38**). Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 38. PLATINUM QCA 12-Month Target Lesion Failure Results by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=100)

	PROMUS Element Stent Male Patients (N=77 Patients, 67 WH Patients)	**PROMUS Element Stent Female Patients (N=23 Patients, 18 WH Patients)**
12-Month TLF	0.0% (0/77)	4.3% (1/23)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (Count/Sample Size)
TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 39 shows PLATINUM QCA primary endpoint and efficacy endpoints for males and females. There were no events through 12 months in the small population of male patients.

Table 39. PLATINUM QCA Primary and Efficacy Endpoint Results by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=100)

	PROMUS Element Stent Male Patients (N=77 Patients, 67 WH Patients)	**PROMUS Element Stent Female Patients (N=23 Patients, 18 WH Patients)**
Primary Endpoint		
Cardiac Death, MI, TLR, ARC ST (definite and probable) through 30 days	0.0% (0/77)	4.3% (1/23)
Efficacy Endpoints		
Peri-procedural Incomplete Apposition	7.5% (5/67)	0.0% (0/21)
9-Month In-stent Late Loss (WH Patients)	0.20±0.24(60) (-0.26,0.87)	0.03±0.25(13) (-0.41,0.55)

Table 39. PLATINUM QCA Primary and Efficacy Endpoint Results by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=100)		
	PROMUS Element Stent Male Patients (N=77 Patients, 67 WH Patients)	**PROMUS Element Stent Female Patients (N=23 Patients, 18 WH Patients)**
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (Count/Sample Size) Abbreviations: ARC=Academic Research Consortium; MI=myocardial infarction; QCA=quantitative coronary angiography; ST=stent thrombosis; TLF=target lesion failure; TLR=target lesion revascularization; WH=workhorse		

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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 did not require advisory panel input.

XII. CONCLUSIONS DRAWN FROM CLINICAL AND NON-CLINICAL STUDIES

The safety and effectiveness of the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) are based on the results obtained from the following measures: biocompatibility; in vivo pharmacokinetics; in vitro engineering testing; coating characterization; chemistry, manufacturing and controls information; in vivo animal testing; sterilization; stability testing; and clinical studies. These tests revealed the following information:

A. SAFETY CONCLUSIONS

The biocompatibility, in vivo pharmacokinetics, and in vivo animal testing conducted demonstrate that the acute and chronic in vivo performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The in vitro engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the everolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

The results of the PLATINUM Clinical Trial Program showed that the principal adverse events rates for the PROMUS Element Plus were similar to those observed for the PROMUS/XIENCE V control group. The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the Directions for Use.

B. EFFECTIVENESS CONCLUSIONS

PLATINUM Workhorse

The results of the PLATINUM Workhorse trial showed that the primary composite endpoint of target lesion failure (TLF) at 12 months post-index procedure was non-inferior to that for the Xience V/PROMUS Everolimus-Eluting Stent control. The composite endpoint of TLF contains both safety and effectiveness components.

PLATINUM Small Vessel

The results of the PROMUS Element Small Vessel showed that the TLF rate at 12 months met the performance goal based on TAXUS Express Stent results from the TAXUS V De Novo trial.

PLATINUM Quantitative Coronary Angiography (QCA) Trial

Endpoints of in-stent late loss at 9 months (determined by QCA) in patients with workhorse target lesions (visual RVD $\geq$2.5 mm and $\leq$4.25 mm and visual lesion length $\leq$24 mm) and post-procedure incomplete apposition (determined by IVUS) were compared to predefined performance goals. For 9-month in-stent late loss, the performance goal was based on historical TAXUS Express stent results. For post-procedure incomplete apposition, the performance goal was based on historical PROMUS (Xience V) post-procedure incomplete apposition data from the SPIRIT III study. Analyses showed that the PROMUS Element stent met the performance goals for both 9-month in-stent late loss and post-procedure incomplete apposition.

C. OVERALL CONCLUSIONS

The clinical testing conducted demonstrated that the PROMUS ELEMENT Everolimus-Eluting Coronary Stent Systems (Monorail and Over-The-Wire) provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. CDRH DECISIONS

CDRH issued an approval order on November 22, 2011. The final conditions of approval cited in the approval order are described below.

1. *Platinum Post-Approval Study*: BSC should conduct a prospective, open-label, multi-center post-approval study, consisting of 2,500 consecutively newly enrolled US patients, with at least 1,000 on-label patients. The data from at least 1,000 newly enrolled on-label patients will be pooled with data from 862 PROMUS PLATINUM WH and SV patients

and 400 PE-PROVE patients, in order to provide a minimum of 2,100 on-label patients with 12 months of outcome data, which will provide at least 80% power to assess the primary endpoint of cardiac death or myocardial infarction (MI). Patients should be evaluated at the timepoints of 30 days, 180 days, and annually through 5-years post-procedure. These study cohorts will be used to assess the primary endpoint (cardiac death or MI at 12 months) and secondary endpoints (stent thrombosis at 5 years and rate of longitudinal stent deformation). In addition, to further elucidate the incidence and etiology of events related to longitudinal stent deformation, the protocol should include:

a. a specific definition for longitudinal stent deformation;

b. questions added to the baseline and procedure forms to capture procedural and anatomic factors, including, but not limited to, whether pre and post-dilatation was performed, whether IVUS was performed, whether other ancillary devices were used and if any resistance was noted during advancement or withdrawal of the ancillary device through a newly implanted stent, target lesion calcification, and tortuosity;

c. a specific question regarding longitudinal stent deformation as part of the device deficiency form as well as additional questions to be addressed by the operator if stent deformation occurs (e.g., the clinical circumstances of the event, the identification of any ancillary or adjunctive devices involved, palliative action taken, if any, and whether malapposition was present prior to stent deformation); and

d. a requirement that angiograms from stent deformation cases be sent to a core laboratory for confirmation that stent deformation occurred, including full analysis of the film. The core laboratory definition for stent deformation will be finalized and included in the protocol as soon as possible, but no later than 60 days following PMA approval.

When appropriate, or as requested by FDA, BSC should submit a PMA supplement to P110010 requesting to update the DFU with the information obtained from this study.

2. *Continued Follow-up of Premarket Cohort*: In addition to the post-approval study enrolling new patients as outlined above, BSC should continue follow-up of the premarket cohorts, consisting of 1,646 patients (Workhorse RCT – 1,530; Small Vessel sub-trial – 94; Human Pharmacokinetics sub-trial – 22 participants). BSC should collect clinical outcomes through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) in the PLATINUM clinical trials. This study will be conducted as per protocol submitted in G080202, and BSC should provide this follow-up data to the PMA as post-approval study reports.

3. The issue of the optimal duration of dual antiplatelet therapy following PCI with drug-eluting stents (DES) remains a critical question that is currently being studied in the DAPT trial. FDA acknowledges that BSC is participating in this trial to address a

condition of approval for the TAXUS Liberté DES (P060008). Patients treated with the PROMUS DES (approved as XIENCE V/PROMUS P070015) are also included in this trial. As the duration of dual antiplatelet therapy is also relevant for the PROMUS Element Plus, BSC should fulfill their commitment to the condition of PMA approval for P060008. When appropriate or as requested by FDA, BSC should submit PMA supplements to the PROMUS Element Plus PMA (P110010) requesting approval to update their DFU to include the data collected in the overall DAPT trial. If BSC does not fulfill the condition of approval for P060008, they should conduct or participate in a separate clinical trial that will develop data to study the duration of dual antiplatelet therapy following implantation of the PROMUS Element Plus DES. When appropriate, or as requested by FDA, BSC should submit PMA supplements to this PMA requesting approval to include these data in a DFU update.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008;117:261-95.

2. Hanratty CG, Walsh SJ. Longitudinal Compression: A "new" Complication with Modern Coronary Stent Platforms – Time to Think Beyond Deliverability? EuroIntervention 2011 (Epub ahead of print)

3. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report From the American Heart Association. Circulation. 2010;121(7):e46-e215.

4. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006; 47(3):S4-S20.