

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™)

PROMUS Element™ Plus Everolimus-Eluting Platinum
Chromium Coronary Stent System (Over-The-Wire)

Promus PREMIER™ Everolimus-Eluting Platinum
Chromium Coronary Stent System (Monorail™)

Promus PREMIER™ Everolimus-Eluting Platinum
Chromium Coronary Stent System (Over-The-Wire)

Device Procode: NIQ

Applicant's Name and Address: Boston Scientific Corporation
One Scimed Place
Maple Grove, MN 55311

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110010/S096

Date of FDA Notice of Approval:

The original PMA (P110010) was approved on November 22, 2011 and is indicated for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 28 mm in length. The SSED to support the indication is available on the CDRH website and is incorporated by reference here:

http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110010b.pdf

A PMA supplement in support of Long Lesion (LL) stent sizes of the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent Systems (P110010/S001) was approved on June 1, 2012 and is indicated for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 24 mm in length. The SSED to support the indication is available on the CDRH website and is incorporated by reference here:

http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110010S001b.pdf

A PMA supplement in support of the Promus PREMIER Everolimus-Eluting Platinum Chromium Coronary Stent System (P110010/S053) was approved on November 21, 2013 and is indicated for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.

PMA supplement (S096) was submitted to support expansion of the indications of the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary System (Monorail and Over-the Wire) and Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-the-Wire), specifically to include the patient population with medically treated diabetes.

I. INDICATIONS FOR USE

The PROMUS Element™ Plus and Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent Systems are indicated for improving luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.

II. CONTRAINDICATIONS

Use of the PROMUS Element™ Plus and Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent Systems 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
- Patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy (see Section 6.2, Pre- and Post-Procedure Antiplatelet Regimen for more information).

III. WARNINGS AND PRECAUTIONS

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

IV. DEVICE DESCRIPTION

The PROMUS Element™ Plus and Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent Systems are device/drug combination products 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 PROMUS Element™ Stent coating consists of two layers, a primer layer and a drug/polymer layer. The primer layer is composed of poly (n-butyl methacrylate) (PBMA). The drug/polymer coating consists of a polymer, PVDF-HFP, and the active pharmaceutical ingredient, everolimus. The PROMUS Element™ Plus and Promus PREMIER Everolimus-Eluting Platinum Chromium Coronary Stent Systems proposed in this supplement are identical to the models previously approved for P110010, P110010/S001, and P110010/S053, with the exception of the diabetic indication addition. Please refer to the device description provided in the original SSED for additional details. The characteristics of the PROMUS Element Plus and Promus PREMIER Stent Systems are described in **Tables 1 and 2**.

The PROMUS Element™ Plus and Promus PREMIER™ Everolimus-Eluting Platinum Chromium Coronary Stent System device characteristics are described in **Tables 1** and **2** below. Design and labeling changes were made to the PROMUS Element Plus stent as part of PMA supplement P110010/S053 which resulted in the Promus PREMIER System. These changes included the addition of proximal stent connectors to some of the stent models, as well as enhancements to the stent delivery system hypotube and bumper tip to align with other commercialized Boston Scientific product lines. Due to the additional connectors on the stent there is a slight increase in the nominal everolimus mass on the coated stent. This increase is considered minimal as is noted below in **Tables 4** and **5** and continues to be within the current process tolerance for the PROMUS Element Plus. The indications for use, stent size matrix (**Table 3**), all materials, drug characteristics, and the drug loading density remain the same for both the PROMUS Element Plus and Promus PREMIER devices.

Table 1: PROMUS Element™ Plus Stent System Product Description

Variable	PROMUS Element Plus Monorail Stent Delivery System	PROMUS Element Plus Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	32, 38	
Available Stent Diameters (mm)	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/cm ² everolimus applied to the stent with a maximum nominal drug content of 241.8 µg on the largest stent (4.00 x 38 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)

Table 2: Promus PREMIER™ Stent System (Monorail™ and Over-The-Wire)

Variable	Promus PREMIER Monorail Stent Delivery System	Promus PREMIER Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38*	
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/cm ² everolimus applied to the stent with a maximum nominal drug content of 241.8 µg on the largest stent (4.00 x 38 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 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	2.1 F (≤0.70 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)

* 38 mm length is not available in 2.25 mm diameter sizes

These devices are available in the following diameters and lengths:

Table 3: PROMUS Element™ Plus and Promus PREMIER Stent Systems (Monorail™ and Over-The-Wire)

			Stent Length								
			8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm*	38 mm**	
Balloon Diameter / Stent Model	SV	2.25 mm	X	X	X	X	X	X	X	N/A	
	Designated Stent Model Separation										
	SWH	2.50 mm	X	X	X	X	X	X	X	LL	LL
		2.75 mm	X	X	X	X	X	X	X	LL	LL
	Designated Stent Model Separation										
	WH	3.00 mm	X	X	X	X	X	X	X	LL	LL
		3.50 mm	X	X	X	X	X	X	X	LL	LL
Designated Stent Model Separation											
LV	4.00 mm	X	X	X	X	X	X	X	LL	LL	
			Stent Length								
			8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm*	38 mm**	
Balloon Diameter / Stent Model	SV	2.25 mm	X	X	X	X	X	X	X	N/A	
	Designated Stent Model Separation										
	SWH	2.50 mm	X	X	X	X	X	X	X	LL	LL
		2.75 mm	X	X	X	X	X	X	X	LL	LL
	Designated Stent Model Separation										
	WH	3.00 mm	X	X	X	X	X	X	X	LL	LL
		3.50 mm	X	X	X	X	X	X	X	LL	LL
Designated Stent Model Separation											
LV	4.00 mm	X	X	X	X	X	X	X	LL	LL	

“X” indicates previously approved in the original PMA

* With the exception of the 2.25 x 32 mm SV stent which was included in the scope of the Original PMA (P110010), the 32 mm models are part of the scope of this PMA supplement.

** With the exception of the 2.25 x 38 mm SV stent which is not available, the 38 mm models are part of the scope of this PMA supplement.

Each PROMUS™ Element Plus or Promus PREMIER™ stent is coated with 100µg/cm² of everolimus per mm stent surface area in a formulation of 1:4.9 (w/w) drug-to-polymer ratio. **Table 4** and **Table 5** provide the nominal total loaded doses of everolimus per nominal stent length/diameter for stent sizes from both the Original PMA and PMA Supplements.

Table 4: PROMUS Element Plus 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	38 mm
Total Loaded Dose Everolimus/ Stent (µg)	SV	38.2	57.3	72.7	91.8	107.2	126.3	145.5	N/A
	SWH	38.9	60.6	78.0	95.4	112.7	130.1	151.8	177.9
	WH	42.0	60.1	84.3	102.4	120.5	138.6	162.8	192.9
	LV	56.1	80.4	104.6	128.8	153.0	177.3	201.5	241.8

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

Table 5: Promus PREMIER 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	38 mm
Total Loaded Dose Everolimus/ Stent (µg)	SV	38.2	57.3	72.7	91.8	107.2	126.3	145.5	N/A
	SWH	39.3	61.1	78.5	95.8	113.2	130.6	152.3	178.4
	WH	42.6	60.7	84.8	102.9	121.1	139.2	163.3	193.5
	LV	57.3	81.5	105.7	129.9	154.1	178.4	202.6	243.0

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

V. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative Practices and Procedures is the same as that presented for the PROMUS Element Plus Original PMA. Reference Section VI Alternative Practices and Procedures, of the Summary of Safety and Effectiveness Data for the PROMUS Element Plus Original PMA P110010.

VI. MARKET HISTORY

As of October 31, 2011, the PROMUS Element™ Everolimus-Eluting Coronary Stent System was commercially available in the following countries listed in **Table 6**.

Table 6: Countries Where PROMUS Element™ is Commercially Available

Albania	Algeria	Andorra	Antigua/Barbuda
Argentina	Armenia	Aruba	Australia
Austria	Azerbaijan	Bahamas	Bahrain
Bangladesh	Barbados	Belgium	Belize
Belarus	Bermuda	Bolivia	Brazil
Brunei	Bulgaria	Chile	China
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	Iran	Iraq
Italy	Jamaica	Jordan	Kenya
Korea	Kuwait	Latvia	Lebanon
Libya	Liechtenstein	Lithuania	Luxembourg
Macedonia	Macau	Malaysia	Malta
Martinique	Mexico	Moldavia	Morocco
Nepal	Myanmar	Netherlands	New Zealand
Nicaragua	Norway	Oman	Pakistan
Palestinian Territory	Panama	Paraguay	Peru
Philippines	Poland	Portugal	Qatar
Romania	Russia	Saudi Arabia	Serbia
Singapore	Slovakia	Sri Lanka	Slovenia
South Africa	Spain	Surinam	Sweden
Switzerland	Syria	Taiwan	Thailand
Trinidad/Tobago	Tunisia	Turkey	Ukraine
United Arab Emirates	Uruguay	Venezuela	Vietnam
Yemen			

As of October 31 2011, approximately 557,532 stents have been distributed outside the United States (OUS). No products have been withdrawn from the market in any country.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of a coronary stent in native coronary arteries.

- 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 deformation, collapse, or fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or re-intervention

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 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 fold lower than that obtained with oral doses (1.5 mg to 20 mg/day).

- 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
- Dysuria
- Dry skin
- Edema (Peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infection (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 CYP3A4
- 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)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Viral, bacterial, and fungal infections
- 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.

For the specific adverse events that occurred in the PLATINUM clinical studies, please see Section X-Summary of Primary Clinical Studies below.

VIII. SUMMARY OF NONCLINICAL STUDIES

No new preclinical studies were submitted or required for the approval of the expanded indication proposed in this PMA Supplement. See original SSED for details.

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

The PLATINUM Clinical Program evaluated the PROMUS Element™ Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions in 5 parallel studies. The Program included the PLATINUM Trial, which comprises 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. Please refer to the original SSED for details on the WH, SV, PK, and QCA studies. Refer to the updated SSED associated with P110010/S001 for details and results of the Long Lesion sub-study.

The PROMUS Element Plus US Post Approval Study included patients with diabetes mellitus and the results of this study provide reasonable assurance of the safety and effectiveness of the PROMUS Element stent systems for use in patients with diabetes. Data from this post approval study are the basis for the indication expansion presented in PMA Supplement P110010/S096. A summary of the post approval study is presented in **Subsection A** below.

PROMUS Element Plus US Post-Approval Clinical Study

A. Study Design

The PROMUS Element Plus US Post-Approval Study was a prospective, open-label, multi-center study designed to observe clinical outcomes in patients receiving the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System, including those patients with diabetes mellitus.

A total of 2683 patients, including 293 PLATINUM-like medically treated diabetic patients, were enrolled across 52 sites in the United States. The study is now considered complete with regard to the primary and diabetic endpoints.

1. Clinical Inclusion and Exclusion Criteria

As this study was a real-world post approval study, no specific inclusion/exclusion criteria were established as part of the approved protocol.

The patient population will include approximately 2,689 consecutive, consented patients.

2. Follow-Up Schedule

Patient follow-up for the study will occur via telephone contact or clinic/office visit at 30-days, 180-days, and annually through 5 years post-index procedure.

Patients with PROMUS Element Plus implant failures will be followed through hospital discharge following the initial attempted index procedure.

The study is considered complete (with regard to the primary endpoint) as all patients have completed the 12-month follow-up.

3. Clinical Endpoints

The primary endpoint for the study was the cardiac death or myocardial infarction rate through 12 months in PLATINUM-like patients receiving the PROMUS Element stent in the PLATINUM WH/SV, PROMUS Element Everolimus-Eluting Coronary Stent System European Post-Approval Surveillance Study (PE-PROVE) and PROMUS Element Plus US Post-Approval studies. The 12-month Cardiac Death (CD)/Myocardial Infarction (MI) rate was to be compared to a performance goal of 3.2% (expected rate of 2.2% plus delta of 1.0%).

PLATINUM-like patients were defined as: all patients without acute myocardial infarction, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation, ostial lesion, severe tortuosity, moderate or severe calcification by visual estimate in target lesion or target vessel proximal to target lesion, three-vessel stenting, cardiogenic shock, left main disease, or acute or chronic renal dysfunction (serum creatinine >2.0 mg/dl or patient on dialysis).

For PLATINUM-like patients, lesion length and RVD should meet one of two criteria: 1) lesion length ≤ 28 mm and diameter ≥ 2.25 mm and < 2.5 mm, or 2) lesion length ≤ 24 mm and diameter ≥ 2.5 mm and ≤ 4.25 mm.

The diabetic endpoint for the study was the target vessel failure (TVF) rate through 12-months in PLATINUM-like medically-treated diabetics receiving the PROMUS Element stent in the PE-PROVE and PROMUS Element Plus US Post-Approval studies. The 12-month TVF rate was to be compared to a performance goal of 12.6% (expected rate of 8.4% plus delta of 4.2%).

B. Accountability of PMA Cohort

At the time of database lock, of the 2683 patients enrolled, 2681 were eligible for the primary and diabetic endpoint analysis. Two patients did not receive any PROMUS Element Plus stents and were not eligible for analysis. Patient disposition for the analysis data set is shown in **Table 7**.

Table 7: Patient Disposition – Follow-up

Variable	PE Plus - Overall (N=2681)
Analysis Data Set	2681
Death ≤ 365 days with no 12-month Clinical Follow-up Performed	60
Eligible for 12-month Clinical Follow-up ^a	2621
12-month Clinical Follow-Up Visit Completed ^b	94.4% (2475/2621)
Office Visit	226
Telephone Contact	2249
No 12-month Clinical Follow-up Visit Performed	146
Premature Discontinuation	42
Withdrew Consent	29
Lost to Follow-up	2
Adverse Event	0
Investigator Discretion	4
Transplantation or Removal of Target Organ	0
Other	1
Death > 365 days	6
Missed 12-month Visit	104
With Later Follow-up Visit Performed	3
No Later Follow-up Visit Performed	101
12-month Clinical Follow-Up or Death ^c	94.6% (2535/2681)

^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 (excludes deaths within 365 days).

^c Includes patients who have died in both the numerator and the denominator.

C. Study Population Demographics and Baseline Parameters

In the overall study population, the average patient age was 63.7 ± 11.1 years and 69.9% of patients were male. In the diabetic subgroup, the average patient age was 63.4 ± 10.1 years and 66.6% of patients were male.

In the overall study population, mean reference vessel diameter (RVD) was 2.94 ± 0.51 mm, mean lesion length was 17.0 ± 10.3 mm and diameter stenosis was $86.7 \pm 10.7\%$. In the diabetic subgroup, RVD was 2.80 ± 0.45 mm, mean lesion length was 12.8 ± 4.7 mm and diameter stenosis was $83.3 \pm 10.4\%$.

D. Safety and Effectiveness Results

The primary endpoint for the PROMUS Element Post Approval Study has been met. The 12-month CD/MI rate of 1.78% was significantly lower than the performance goal of 3.2%.

The diabetic endpoint for this study has also been met. The TVF rate of 4.22% through 12-months in PLATINUM-like medically-treated diabetics receiving the PROMUS Element stent in the PE-PROVE and PROMUS Element Plus US Post-Approval studies was significantly lower than the performance goal of 12.6%.

The PLATINUM-Like population and PLATINUM-Like medically-treated diabetic population for the 12 month primary endpoint and 12 month primary diabetic endpoint included patients from both the PE-Prove Study and PROMUS Element Plus US Post-Approval Study. **Table 8** presents a comparison of the 12-month TVF rates for the PE-Prove and PROMUS Element Plus Post Approval Studies. Some baseline differences in patient characteristics may have existed between the two studies.

Additional study results are presented in **Table 9** and **Table 10** below.

Table 8: PE-Prove and PROMUS Element Plus Post-Approval Study 12-month TVF Rates

Medically-treated Diabetic Endpoint	PE-Prove (N=59 Patients)	PE-Plus (N=293 Patients)	P-value
12-Month TVF (PLATINUM-Like* Medically-Treated Diabetic Patients)	8.9 (5/56)	3.3% (9/276)	0.068
<p>*PLATINUM-like patients were defined as: all patients without acute myocardial infarction, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation, ostial lesion, severe tortuosity, moderate or severe calcification by visual estimate in target lesion or target vessel proximal to target lesion, three-vessel stenting, cardiogenic shock, left main disease, or acute or chronic renal dysfunction (serum creatinine >2.0 mg/dl or patient on dialysis). For PLATINUM-like patients, lesion length and RVD should meet one of two criteria: 1) lesion length ≤28 mm and diameter ≥2.25 mm and <2.5 mm, or 2) lesion length ≤24 mm and diameter ≥2.5 mm and ≤4.25 mm.</p> <p>All composite event rates related to MI are based on the Platinum Trial MI definition.</p>			

Table 9: PROMUS Element Plus Post-Approval Study Primary Endpoint and Diabetic Endpoint – Performance Goal Analyses

Primary Endpoint	PLATINUM WH/SV (N=862)	PE-Prove (N=269)	PE-Plus (N=776)	Overall (N=1907)	Upper 1-Sided 95% CL	PG	P-value
12-Month Cardiac Death/MI (PLATINUM-Like* Patients)	2.1% (18/851)	3.4% (9/263)	0.8% (6/741)	1.8% (33/1855)	2.3%	3.2%	<.0001
Medically-treated Diabetic Endpoint	PE-Prove + PE Plus (N=352)		Upper 1-Sided 95% CL	PG	P-value		
12-Month TVF (PLATINUM-Like* Medically-Treated Diabetic Patients)	4.2% (14/332)		6.0%	12.6%	<.0001		
12-Month TVF (PLATINUM-Like* Medically-Treated Diabetic Patients) [Utilizing CK-MB MI definition] **	4.8% (16/332)		6.8%	12.6%	<.0001		
<p>*PLATINUM-like patients were defined as: all patients without acute myocardial infarction, graft stenting, chronic total occlusion, in-stent restenosis, failed brachytherapy, bifurcation, ostial lesion, severe tortuosity, moderate or severe calcification by visual estimate in target lesion or target vessel proximal to target lesion, three-vessel stenting, cardiogenic shock, left main disease, or acute or chronic renal dysfunction (serum creatinine >2.0 mg/dl or patient on dialysis). For PLATINUM-like patients, lesion length and RVD should meet one of two criteria: 1) lesion length ≤28 mm and diameter ≥2.25 mm and <2.5 mm, or 2) lesion length ≤24 mm and diameter ≥2.5 mm and ≤4.25 mm.</p> <p>Note: PLATINUM-like population for the Primary Endpoint at 12 months includes PROMUS Element patients from</p>							

PreMarket Approval Supplement P110010/S096
PROMUS Element™ Plus and Promus PREMIER™

the PLATINUM trials (WH and SV), PLATINUM-like patients from PE-Prove, and PLATINUM-like patients from PROMUS Element Plus US Post-Approval Study.

Note: The PLATINUM-Like medically-treated diabetic population for the diabetic endpoint TVF at 12 months includes PLATINUM-like medically-treated diabetic patients from PE-Prove and PROMUS Element Plus US Post-Approval Study.

All composite event rates related to MI are based on the Platinum Trial MI definition.

** Myocardial Infarctions used in this analysis were based on a definition of CK-MB > 3x ULN. Events from PE Plus trial were CEC adjudicated to this definition, and events from PE-Prove were evaluated based on all available cardiac enzyme data.

Table 10: PROMUS Element Plus Post-Approval Study 12-Month Clinical Results

Effectiveness and Safety Measures	PE Plus - Overall (N=2681 Patients)	PLATINUM-Like (N=776 Patients)	
		Diabetic (N=293 Patients)	Non-Diabetic (N=483 Patients)
MACE	6.9% (177/2554)	3.6% (10/276)	2.8% (13/465)
Related to PROMUS Element Plus	4.7% (119/2554)	0.7% (2/276)	1.5% (7/465)
All Death or MI	3.2% (82/2554)	1.4% (4/276)	1.3% (6/465)
Cardiac Death or MI	2.3% (59/2554)	0.7% (2/276)	0.9% (4/465)
Related to PROMUS Element Plus	1.8% (46/2554)	0.4% (1/276)	0.4% (2/465)
Related to Target Vessel	2.0% (51/2554)	0.4% (1/276)	0.4% (2/465)
Death	2.3% (60/2554)	1.4% (4/276)	1.1% (5/465)
Cardiac Death	1.4% (37/2554)	0.7% (2/276)	0.6% (3/465)
Related to PROMUS Element Plus	1.3% (33/2554)	0.4% (1/276)	0.4% (2/465)
Related to Target Vessel	1.3% (33/2554)	0.4% (1/276)	0.4% (2/465)
Non-Cardiac Death	0.9% (23/2554)	0.7% (2/276)	0.4% (2/465)
Myocardial Infarction	1.1% (28/2554)	0.4% (1/276)	0.4% (2/465)
Related to PROMUS Element Plus	0.7% (17/2554)	0.4% (1/276)	0.0% (0/465)
Related to Target Vessel	0.9% (23/2554)	0.4% (1/276)	0.0% (0/465)
Q-Wave MI	0.2% (5/2554)	0.0% (0/276)	0.2% (1/465)
Related to PROMUS Element Plus	0.1% (3/2554)	0.0% (0/276)	0.0% (0/465)
Related to Target Vessel	0.2% (4/2554)	0.0% (0/276)	0.0% (0/465)
Non Q-Wave MI	0.9% (23/2554)	0.4% (1/276)	0.2% (1/465)
Related to PROMUS Element Plus	0.5% (14/2554)	0.4% (1/276)	0.0% (0/465)
Related to Target Vessel	0.7% (19/2554)	0.4% (1/276)	0.0% (0/465)
TVR	5.6% (142/2554)	3.3% (9/276)	2.2% (10/465)

Effectiveness and Safety Measures	PE Plus - Overall (N=2681 Patients)	PLATINUM-Like (N=776 Patients)	
		Diabetic (N=293 Patients)	Non-Diabetic (N=483 Patients)
Related to PROMUS Element Plus	3.5% (90/2554)	0.7% (2/276)	1.1% (5/465)
TVF	6.7% (170/2554)	3.3% (9/276)	2.6% (12/465)
Related to PROMUS Element Plus	4.7% (119/2554)	0.7% (2/276)	1.5% (7/465)
ARC ST (Definite/Probable)	0.7% (19/2554)	0.4% (1/276)	0.2% (1/465)
Related to PROMUS Element Plus	0.7% (19/2554)	0.4% (1/276)	0.2% (1/465)
Related to Target Vessel	0.7% (19/2554)	0.4% (1/276)	0.2% (1/465)

Numbers are % (count/sample size).
Abbreviations: ARC=Academic Research Consortium; MI=myocardial infarction; TVR=target vessel revascularization; TVF=target vessel failure; ST=stent thrombosis
All MI rates and composite event rates related to MI are based on the Platinum Trial MI definition.
If an event could not be determined with certainty whether it was related to the target vessel or PROMUS Element Plus stent it was considered as related.

E. Financial Disclosures

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 52 Principal Investigators, of which none were full-time or part-time employees of the sponsor and three (including one Sub-Investigator) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

X. 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 substantially duplicates information previously reviewed by this panel.

XI. CONCLUSIONS DRAWN FROM CLINICAL AND NON-CLINICAL STUDIES

The safety and effectiveness of the PROMUS Element™ Plus and Promus PREMIER Everolimus-Eluting Platinum Chromium Coronary Stent Systems (Monorail™ and Over-The-Wire) is 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. The PROMUS Element™ Plus Post Approval Study provides safety and effectiveness data in support of use of these devices in patients with diabetes mellitus.

A. Effectiveness Conclusions

The results of the PROMUS Element Plus US Post-Approval Study showed that the cardiac death or myocardial infarction rate through 12 months in PLATINUM-like patients receiving the PROMUS Element stent in the PLATINUM WH/SV, PROMUS Element Everolimus-Eluting Coronary Stent System European Post-Approval Surveillance Study (PE-PROVE) and PROMUS Element Plus US Post-Approval studies met the performance goal of 3.2% (expected rate of 2.2% plus delta of 1.0%).

The diabetic endpoint of TVF rate through 12-months in PLATINUM-like medically-treated diabetics receiving the PROMUS Element stent in the PE-PROVE and PROMUS Element Plus US Post-Approval studies also met the performance goal of 12.6% (expected rate of 8.4% plus delta of 4.2%).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA Supplement approval as described above. The conclusions based on the nonclinical findings were previously described for the original PMA submission (P110010).

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA supplement approval as described above. The PROMUS Element Plus US Post-Approval Study showed that in patients with symptomatic heart disease or documented silent ischemia due to de novo lesions in native coronary arteries, including patients with diabetes mellitus, the adverse event rates for the PROMUS Element™ stents were clinically acceptable. Given the available supportive nonclinical and clinical data regarding the stent provided in both the Original PMA and this PMA Supplement, the safety decision based on the PROMUS Element Plus US Post-Approval Study was considered acceptable.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA Supplement approval as described above. PROMUS Element Plus has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease or silent ischemia. Rates of target lesion failure (TLF – defined as cardiac death related to the target vessel, MI related to the target vessel or target lesion revascularization) are non-inferior with PROMUS Element Plus in comparison to the TAXUS Express 32 mm drug-eluting stent.

Additional factors were considered in determining probable risks and benefits for the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) device. Key clinical data supporting the safety and effectiveness of PROMUS Element Plus, including in patients with diabetes mellitus, were obtained from both a large, randomized controlled trial, and from a single-arm, non-randomized post-market study where the effectiveness outcome (TVF) was compared to a historical control. Important markers of safety, including death, MI, and stent thrombosis were low. Alternative treatments for coronary artery disease, including other coronary stents and both medical and surgical therapy, are available and the risks and benefits of these therapies were carefully considered. The risks and benefits of the PROMUS Element Plus were found to be similar to the risks and benefits of other approved drug-eluting stents.

In conclusion, given the available information above, the data support that for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to de novo lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length, including those patients

with diabetes mellitus, the probable benefits outweigh the probable risks, and adds to the treatment options available to patients with symptomatic coronary artery disease.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XII. CDRH DECISIONS

CDRH issued an approval order on

XIII. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

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

Post-approval Requirements and Restrictions: See Approval Order.