

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System

Device Trade Name: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™)

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

Device Procode: NIQ

Applicant's Name and Address: Boston Scientific Corporation
300 Boston Scientific Way
Marlborough, MA 01752

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150003

Date of FDA Notice of Approval: October 2, 2015

II. INDICATIONS FOR USE

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients with symptomatic heart disease, stable angina, unstable angina, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.

III. CONTRAINDICATIONS

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

- 316L stainless steel or, platinum, chromium, iron, nickel or molybdenum;
- everolimus or structurally-related compounds; and/or
- the polymer or their individual components.

Coronary Artery Stenting is contraindicated for use in:

- 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY) is a device/drug combination product that provides a mechanical structure for vascular lumen support (primary mode of action) and a pharmacological agent (everolimus) targeted towards reducing the injury response. The System consists 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 bioabsorbable polymer, poly (D,L-lactide-co-glycolide) (PLGA), and the active pharmaceutical ingredient, everolimus. The characteristics of the SYNERGY stent system are described in **Table V-T1**.

Table V-T1: SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System Product Description

	SYNERGY Monorail Stent Delivery System	SYNERGY 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	0.074 mm for diameters 2.25 mm to 2.75 mm 0.079 mm for diameters 3.00mm to 3.50 mm 0.081 mm for diameter of 4.00 mm	
Drug Product	An abluminal (outer surface of the stent) coating of a polymer carrier with approximately 1 µg of everolimus per mm ² of total stent surface area with a maximum nominal drug content of 287.2 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)	

	SYNERGY Monorail Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Catheter Shaft Outer Diameter	Proximal: 2.1 F (0.70 mm) Distal: 2.25 mm – 2.75 mm: 2.6F (0.90 mm) 3.00 mm (8 – 28 mm): 2.6F (0.90mm) 3.00 mm (32 – 38 mm): 2.7F (0.95 mm) 3.50 mm (8 – 20 mm): 2.6F (0.90 mm) 3.50 mm (24 – 38 mm): 2.7F(0.95 mm) 4.00 mm: 2.7F (0.95 mm)	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)

A. Device Component Description

The SYNERGY stent is comprised of a Platinum Chromium Alloy (PtCr). Similar to other metallic stents manufactured by BSC, the stent component is laser cut into a specific geometric pattern which consists of serpentine rings connected by links that are highly polished to a uniform rounded surface.

Three separate stent models were designed in specific size ranges. A stent model is defined as a variation of a specific geometry pattern designed for various vessel diameters. The three models are defined below:

- Small Vessel (SV): 2.25 mm, 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 V.A-T2** below.

Table V.A-T2: SYNERGY U.S. Commercial Matrix (Monorail and Over-The-Wire)

		Stent Length								
		8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	38 mm	
Stent Model/ Balloon Diameter	SV	2.25 mm	X	X	X	X	X	X	X	X
		2.50 mm	X	X	X	X	X	X	X	X
		2.75 mm	X	X	X	X	X	X	X	X
	WH	3.00 mm	X	X	X	X	X	X	X	X
		3.50 mm	X	X	X	X	X	X	X	X
	LV	4.00 mm	X	X	X	X	X	X	X	X

B. Drug Component Description

The SYNERGY stent drug matrix is composed of the bioabsorbable polymer poly (D,L-lactide-co-glycolide) (PLGA) and the anti-proliferative drug everolimus. The drug to polymer formulation is 45:55 (w/w).

B1. Everolimus

The active pharmaceutical ingredient in the SYNERGY stent is everolimus. The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin, and its chemical structure is provided in **Figure V.B.1-F1**. The nominal total loaded dose of everolimus per nominal stent length/diameter is shown in **Table V.B.1-T1**.

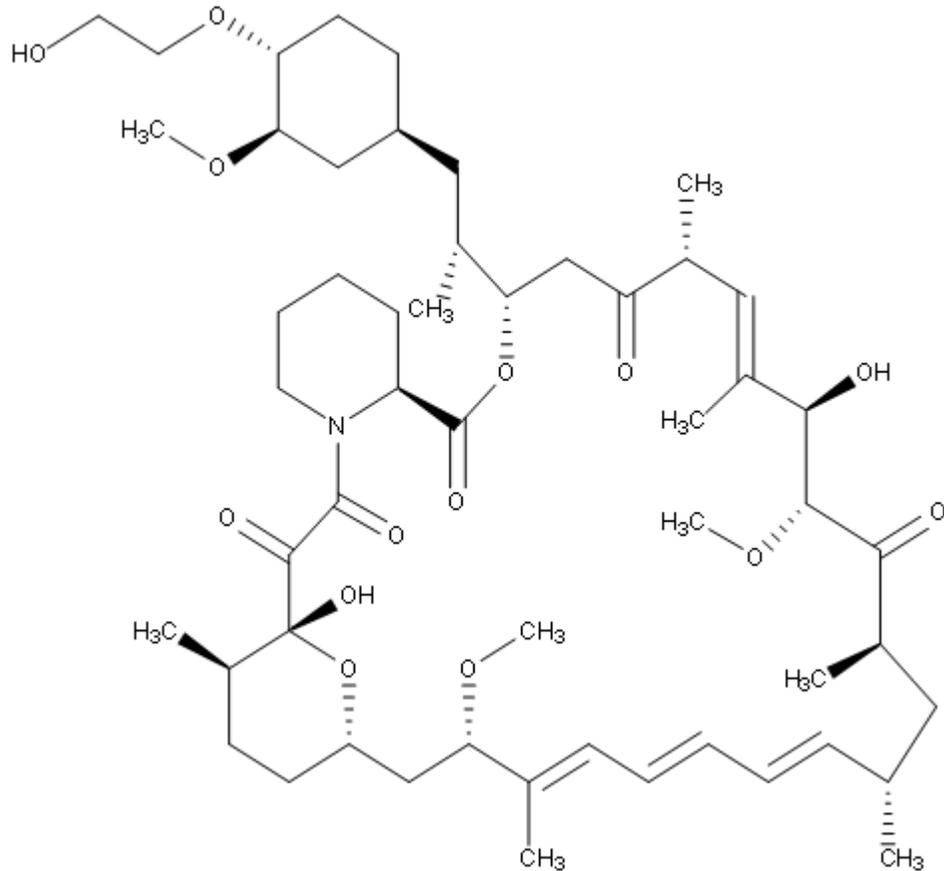


Figure V.B.1-F1: Structure of Everolimus

Table V.B.1-T1: Nominal Total Loaded Dose of Everolimus (μg) per Nominal Stent Length and Diameter

		Stent Length							
Design	Stent Model	8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm	38 mm
Total Drug Content/ Stent (μg)	SV	38.9	58.3	77.6	96.9	121.1	140.5	159.8	188.9
	WH	46.5	66.3	92.7	112.5	132.3	158.7	178.5	211.6
	LV	67.5	96.2	124.8	153.5	182.2	210.8	239.5	287.2

		Stent Length							
Total Coat Weight/ Stent (µg)	SV	87	132	174	218	273	316	360	426
	WH	104	149	209	254	298	358	403	477
	LV	152	217	281	346	411	475	539	647

SV – Small Vessel (2.25 mm, 2.50 mm, and 2.75 mm)

WH – Workhorse (3.00 mm and 3.50 mm)

LV – Large Vessel (4.00 mm)

B2. Inactive Ingredient

Polymer—poly (DL-lactide-co-glycolide) (PLGA)

SYNERGY is abuminally coated with a bioabsorbable coating. The coating consists of bioabsorbable PLGA polymer and everolimus. The PLGA polymer provides controlled and sustained release of available everolimus through the intended time frame, during which the polymer is reabsorbed into the body. The chemical structure of PLGA is shown in **Figure V.B.2-F1**.

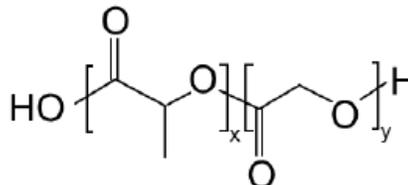


Figure V.B.2-F1: Structure of PLGA

C. Mechanism of Action of Everolimus

On a cellular level, everolimus inhibits, in a reversible manner, growth factor-stimulated cell proliferation. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian target of rapamycin) this finding suggests that, the everolimus-FKBP-12 complex binds to and thus interferes with the function of FRAP. FRAP is a key regulatory protein which governs cell metabolism, growth and proliferation. Disabling FRAP function explains the cell cycle arrest at the late G1 stage caused by everolimus.

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. MARKETING HISTORY

As of January 30, 2014, approximately 31,943 SYNERGY stents have been distributed outside the United States. **Table VII-T1** lists countries where the product is currently commercially available. No products have been withdrawn from the market in any country for any reason.

Table VII-T1: Countries with SYNERGY Commercial Availability

Algeria	Hungary	Norway
Argentina	Iceland	Pakistan
Australia	India	Panama
Austria	Indonesia	Peru
Bahrain	Iraq	Philippines
Bangladesh	Ireland	Poland
Belgium	Italy	Portugal
Bosnia-Herz.	Kosovo	Romania
Brazil	Kuwait	Saudi Arabia
Bulgaria	Latvia	Singapore
Chile	Libya	Slovakia
Colombia	Liechtenstein	Slovenia
Cyprus	Lithuania	South Africa
Czech Republic	Luxembourg	Spain
Denmark	Macau	Sweden
Ecuador	Macedonia	Switzerland
Estonia	Malaysia	Thailand
Finland	Malta	Tunisia
France	Mexico	United Arab Emirates
Germany	Morocco	Uruguay
Great Britain	Nepal	Venezuela
Greece	Netherlands	White Russia
Hong Kong	New Zealand	

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 device(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

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- 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

There may be other potential adverse events that are unforeseen at this time.

Please refer to the observed events for the EVOLVE II clinical study, which are presented in **Section X: Summary of Clinical Studies**.

IX. SUMMARY OF PRECLINICAL 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 PLGA polymer;
- The drug substance (i.e., everolimus); and
- 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 materials and components of the SYNERGY 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 drug and polymer coated stents, and stent delivery systems. These test articles were manufactured with the final proposed commercial process (i.e., surface treatment, coating processing, amount of drug/polymer coating, and sterilization). In all of these test systems, the materials were biocompatible and produced no greater response than the negative control employed in each test system.

All biocompatibility testing was conducted in accordance with:

- FDA Guidance for Industry: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010
- Draft FDA Guidance for Industry: Coronary Drug-Eluting Stents - Nonclinical and Clinical Studies, March 2008
- Draft FDA Guidance for Industry: Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, April 23, 2013
- Good Laboratory Practices Regulations (§21CFR 58)

The biocompatibility studies that have been conducted in support of the SYNERGY stent are summarized in **Table IX.A-T1**.

Table IX.A-T1: Biocompatibility Tests Summary

Test Name	Test Description	Test Article and Results
Cytotoxicity	ISO 10993-5: <i>In Vitro</i> Cytotoxicity (MEM Elution)	▪ Stent and delivery systems (MR and OTW): Pass (non-cytotoxic)
	ISO 10993-5: <i>In Vitro</i> Cytotoxicity (Direct Contact)	▪ Stent: Pass (non-cytotoxic)

Test Name	Test Description	Test Article and Results
Sensitization	ISO 10993-10: Sensitization (Guinea Pig Maximization)	▪ Stent and delivery systems (MR and OTW): Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Irritation (Injection)	▪ Stent and delivery systems (MR and OTW): Pass (non-irritant)
Systemic Toxicity	ISO 10993-11: Systemic Toxicity (Acute)	▪ Stent and delivery systems (MR and OTW): Pass (non-toxic)
	ISO 10993-11: Systemic Toxicity (Material-Mediated Rabbit Pyrogen)	▪ Stent and delivery systems (MR and OTW): Pass (non-pyrogenic)
Genotoxicity	ISO 10993-3: Bacterial Reverse Mutation Assay (Ames Assay)	▪ Stent and delivery systems (MR and OTW): Pass (non-mutagenic)
	ISO 10993-3: Mouse Lymphoma	▪ Stent and delivery systems (MR and OTW): Pass (non-mutagenic, non-clastogenic)
	ISO 10993-3: <i>In Vivo</i> Mouse Micronucleus Test	▪ Stent: Pass (non-mutagenic)

Test Name	Test Description	Test Article and Results
Chemical Characterization – Extractables/ Leachables/ Corrosion	ISO 10993-9 and -18 Chemical Characterization Extractables: ICP-MS, GC-MS, LC-MS, Ion Chromatography	▪ Bare Metal Stent: Pass
	ISO 10993-9 and 18 Residues and Leachables Characterization	▪ Bare Metal Stent: Pass
	USP <661> Physiochemical Test for Plastics	▪ Delivery systems (MR and OTW): Pass
Latex	Latex Testing ASTM D6499-12 ELISA Assay	▪ Stent and delivery systems (MR and OTW): Below level of detection
Hemocompatibility	ISO 10993-4: Direct Hemolysis	▪ Stent and delivery systems (MR and OTW): Pass (non-hemolytic)
	ISO 10993-4: Indirect Hemolysis (Extract)	▪ Stent and delivery systems (MR and OTW): Pass (non-hemolytic)
	ISO 10993-4: <i>In Vitro</i> Hemocompatibility	▪ Stent and delivery systems (MR and OTW): Pass (comparable to control)
	ISO 10993-4: Partial Thromboplastin Time (PTT)	▪ Stent and delivery systems (MR and OTW): Pass (Results comparable to negative control)
	ISO 10993-4: Complement Activation C3a & SC5b-9 Assay	▪ Stent and delivery systems (MR and OTW): Pass (negative for C3a and SC5b-9 assays)
	ISO 10993-4: <i>In Vivo</i> Thromboresistance (Porcine)	▪ Stent: Pass (no thrombus at 90 days)
Carcinogenicity	ISO 10993-3: Carcinogenicity (rasH2-Transgenic Mice)	▪ Not Directly Tested: See Justification below
Reproductive Toxicity	ISO 10993-3: Reproductive Toxicity Teratology (Rat)	▪ Not Directly Tested: See Justification below
Implantation/Chronic Toxicity	ISO 10993-11: Chronic Toxicity/ ISO 10993-6: Implantation (Rat)	▪ Stent: Pass (non-toxic, non-irritating)
Toxicokinetics	ISO 10993-16: Toxicokinetics (Porcine)	▪ Stent: Pass (non-toxic)

Chronic toxicity, *in vivo* thrombogenicity, toxicokinetics, and implantation of a test article in the porcine model was provided to support the vascular safety and compatibility of the SYNERGY product. See **Section IX.G: Animal Studies**.

Carcinogenicity and Reproductive toxicity testing on the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System were omitted based on the following:

- SYNERGY was tested for genotoxicity (Ames mutagenicity, *in vitro* mouse lymphoma and *in vivo* mouse micronucleus assays); negative results of genotoxicity testing suggest that the likelihood of the stent material to cause a carcinogenic response is minimal.

- In addition, the levels of ten elements (As, Co, Cr, Fe, Mo, Ni, Pb, Pt, Si, and V) were below the Quantitation Limit in a leachable study of the bare metal stent using Inductively Coupled Plasma analysis with Optical Emission Spectrometry (ICP-OES). No manufacturing residues could be found on bare metal stent using Pyrolysis GCMS and solvent extraction followed by GCMS. Chemical safety assessments conducted on the SS Pt-Cr material and potential manufacturing residues indicate that “the PERSS material as used in cardiovascular stents do not pose a health and safety concern to patients” As the SYNERGY bare metal stent is equivalent to the Element bare metal stent it can be concluded that the manufactured SYNERGY bare metal stent does not pose a carcinogenic risk to patients.
- The carcinogenic potential of everolimus has been addressed by Abbott Vascular in a previous study. The XIENCE stent coated with PBMA/PVDF-HFP was tested in transgenic mice (ras H-2) which showed no evidence of tumor formation. Also the SYNERGY stent containing everolimus has passed not only *in vitro* (Ames and Mouse Lymphoma) but also *in vivo* (Mouse Micronucleus) genotoxicity assays. The carcinogenic potential of everolimus does not appear to change in the presence of PLGA as all studies passed; therefore no additional carcinogenicity investigations were conducted. A GLP polymer safety study, literature safety assessment, and *in vitro* characterization of PLGA degradation products demonstrate that the polymer is non-carcinogenic.

The potential risk for vascular thrombosis due to use of the delivery system was deemed acceptable based upon an evaluation of a representative test article in the canine model. Use of the vascular study in the canine model was deemed acceptable because the materials of manufacture, design, and surface geometries for the delivery system are similar to the commercially available Emerge PTCA Dilatation catheter (K113220, cleared March 22, 2012).

Based upon the biocompatibility testing and safety data for everolimus, PLGA, product materials, it can be concluded that the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System is biocompatible for its intended use.

B. In Vitro Engineering Testing

In vitro engineering testing on the SYNERGY 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, 18 April 2010
- FDA Draft Guidance for Industry and Staff: Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies, March 2008
- FDA Guidance for Industry and Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment, 21 August 2008

- Draft FDA Guidance for Industry: Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 30 August 2013

The *in vitro* engineering studies conducted are summarized in **Table IX.B-T1**. “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 SYNERGY Everolimus-Eluting Platinum Chromium stent as shown in **Section IX.C: Coating Characterization Testing**.

Table IX.B-T1: 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 SYNERGY stents were tested to determine the corrosion susceptibility using cyclic potentiodynamic polarization per ASTM F2129-08, “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 bare metal 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 Crevice Corrosion was assessed on “as manufactured” coated SYNERGY stents after pulsatile fatigue cycling. The corrosion series testing indicated that the corrosion resistance characteristics of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary stent met product specification.	Pass
Nickel Elution	As outlined in Section IV.E of the FDA Draft Guidance for Industry “ Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, the potential of nickel ion release is to be considered for devices containing nitinol. The SYNERGY combination product is comprised of a platinum chromium alloy stent and therefore is no subject to nickel ion release testing. Acceptable performance of SYNERGY in testing of potentiodynamic, crevice, galvanic and fretting corrosion demonstrates sufficient corrosion resistance and an adequate passivation layer to justify per the guidance therefore there is no need for additional nickel ion release testing.	N/A
Stent Dimensional and Functional Attributes		
Dimensional Verification	To measure and inspect the stent to document that the stent dimensional specifications meet the product design requirements, including un-expanded stent dimensions, expanded diameter and length (see Stent Delivery System Dimensional and Functional Attributes testing). All product met specifications.	Pass

Test	Description of Test	Conclusion
Percent Surface Area	Stent surface coverage as a function of stent diameter was measured for the SYNERGY 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 foreshortening test determined the change in length of the stent between the catheter-mounted condition and the condition in which the stent was expanded (deployed) to the nominal diameter and to stent over-expansion limits. All product met 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.	Pass
Stent Overexpansion	The purpose of this testing is to verify the stent integrity post-stent deployment when expanded above unconstrained diameter. No stent exhibited any strut fracture when visually examined at a minimum of 30X following overexpansion.	Pass
Radial Stiffness and Radial Strength (Compression Resistance)	Testing was conducted to determine the ability of the stent to resist deformation under radial loads.	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
Magnetic Resonance Imaging (MRI) Safety and Compatibility	<p>The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent has shown to be MR Conditional (poses no known hazards under specified conditions) for single and overlapped conditions up to 75mm. A patient with this device can be safely scanned in a:</p> <p>Magnetic Resonance system meeting the following conditions:</p> <ul style="list-style-type: none"> • Static magnetic field of 3.0 and 1.5 Tesla only • Maximum spatial gradient magnetic field of 2300 gauss/cm (23 T/m) • Maximum Magnetic Resonance system reported, whole body averaged specific absorption rate (SAR) of <2 W/kg (Normal Operating Mode) <p>Under the scan conditions defined above, the SYNERGY Stent is expected to produce a maximum temperature rise of 3.1°C after 15 minutes of continuous scanning.</p> <p>In non-clinical testing, the image artifact caused by the device extends approximately 10mm from the SYNERGY Stent when imaged with a gradient echo pulse sequence and a 3.0 Tesla MRI system</p> <p>The SYNERGY 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 MR Conditional beyond these conditions</p> <p>3.0 Tesla Temperature Information</p> <p>Non-clinical testing of RF-induced heating was performed at 123 MHz in a 3</p>	Pass

Test	Description of Test	Conclusion
	<p>T General Electric Medical Systems MR system, Model Sigma Hdxt, software version 15.0 M4 0910.a. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.49 S/m. The phantom average SAR was calculated using calorimetry to be 2.3 W/kg. The maximal <i>in vitro</i> temperature rise was calculated as 2.6°C for a measured stent length up to 75 mm with the whole body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow. <i>In vivo</i>, 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.</p> <p>1.5 Tesla Temperature Information Non-clinical testing of RF-induced heating was performed at 64 MHz in a 1.5 T 64 MHz RF laboratory system, Medical Implant Test System (MITS) 1.5, Zurich Medtech AG (ZMT), Model Medical Implant Test Systems 1.5, software version MITS-DUAL BAND 1.2.5.2 whole body coil MR scanner. RF power was applied for 15 minutes and the measured conductivity of the phantom material was about 0.50 S/m. The phantom average SAR was calculated using calorimetry to be 2.3 W/kg. The maximal <i>in vitro</i> temperature rise was calculated as 3.1°C for a measured stent length up to 75 mm with the whole body SAR scaled to 2.0 W/kg. The calculations did not include the cooling effects due to blood flow. <i>In vivo</i>, 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.</p> <p>The actual <i>in vivo</i> rise is expected to be less than these values as the calculations did not include the cooling effects due to blood flow in the lumen of the stent and blood perfusion in the tissue outside the stent.</p> <p><i>In vivo</i>, 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. No tests have been performed on possible nerve or other tissue stimulation possible to be activated by strong gradient magnetic fields and resulting induced voltages.</p> <p>Image Artifact Information The calculated image artifact extends approximately 8 mm from the perimeter of the device diameter and 6 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 10 mm beyond the perimeter of the diameter and 9 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 2.6.3.7 2101-11-2412 MR system.</p> <p>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.</p>	
Radiopacity	The radiopacity of the stent was assessed through porcine model evaluations of stent positioning, expansion, and delivery system removal. The stent exhibits clinically acceptable radiopacity.	Pass

Test	Description of Test	Conclusion
Stent Dimensional and Functional Attributes, continued		
Stent Axial Strength	The ability of the stent to withstand length change after being subjected to a point-load force was tested. All product met specifications.	Pass
	The axial strength of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent system was characterized in a constrained state with malapposition against commercially available Promus Premier and Resolute Integrity for force at work at 3 mm of displacement. The results demonstrate comparable performance to commercially marketed product.	Pass
Delivery System Dimensional and Functional Attributes		
Delivery, Deployment and Retraction	The delivery, deployment and retraction of the delivery 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 stent system could be delivered to the target location, deployed, and retracted, thus meeting required acceptance criteria.	Pass
Balloon Rated Burst Pressure (RBP)	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	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
Balloon Inflation and Deflation Time	Stent systems across the range of balloon lengths and diameters were evaluated for deflation and inflation times. Results indicated that the product specifications were met.	Pass
Catheter Bond Strength	Representative sizes of the stent delivery system were tested to determine the balloon bond, tip bond, and full unit tensile strength of the delivery system. All stent systems met or exceeded the minimum specifications for full unit tensile strength and balloon bond.	Pass
Tip Tensile (Tip Pull)	Stent delivery systems were tested to determine the tip bond strength. All product met specifications.	Pass
Flexibility and Kink	Stent delivery systems were evaluated to determine the ability of the delivery system to withstand kinking. All product specifications were met.	Pass
Catheter Coating Integrity and Thickness	The acute coating integrity of the stent delivery system coating was evaluated via the results of a series of acute <i>in vitro</i> tests (baseline and simulated use). The test results demonstrated that the hydrophilic coating displays acceptable coating integrity.	Pass
Stent Securement for Unsheathed Stents	Stent systems were evaluated to assess the forces required to displace a 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.	Pass
Non-Coaxial Withdrawal into a Simulated Guiding Catheter	Stent systems were evaluated for performance during withdrawal of a catheter with a mounted stent non-coaxially into a simulated guide catheter tip following a repeated track conditioning step. Results indicated that the product specifications were met for stent securement. All samples met the specification.	Pass

Test	Description of Test	Conclusion
Stent/Balloon Catheter Withdrawal Resistance	Testing was conducted to verify that the 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 stent coating was assessed via a series of acute <i>in vitro</i> tests performed on the SYNERGY coated stent (baseline and simulated use). The test results demonstrate that the PLGA/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 SYNERGY stent coating. The 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 interface 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 stent fatigue failures will not occur over 400 million cycles (10-years) of loading.	Pass
Accelerated Durability Testing	Accelerated durability testing was performed on the SYNERGY 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 Overlapping Pulsatile Fatigue on a Curve. All tested stents were free from fatigue induced strut fracture. The coated stent met the 10 year accelerated fatigue resistance specification.	Pass
Particulate Evaluation (Simulated Use)	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 until the point where particulation dropped to negligible levels with a plateau in the cumulative particulates observed from the biodegradable stent coating.	Pass

C. Coating Characterization Testing

The coating characterization testing conducted on the SYNERGY stent coating is summarized in **Table IX.C-T1**.

Table IX.C-T1: Coating Characterization Testing

Test	Description of Test
Materials/Chemical Analysis – Polymer	Polymer components were tested to ensure conformity to raw material specifications.
Material/Chemical Analysis – Drug	Drug substance was tested to ensure conformity to raw material specifications.

Drug Loading Density	Dose per unit area was calculated.
Coating Thickness Uniformity	Testing was conducted to verify the 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 stent coating.
Drug Content	Assay was conducted to quantitatively determine the total amount of the drug substance, everolimus, on the SYNERGY drug constituent part.
Impurities and Degradation Products	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the SYNERGY drug constituent part.
Drug Release	Assay was developed to measure the <i>in vitro</i> drug release of everolimus from the SYNERGY drug constituent part.
Particulates	Particulate levels were evaluated for the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System post tracking, deployment, and fatigue.

D. Chemistry Manufacturing Control (CMC) Testing

Each batch of finished devices undergoes testing for release and distribution. This testing is summarized in **Table IX.D-T1**. Where applicable, the test methods follow International Conference on Harmonization (ICH) Guidelines. Information to support the stability of SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System is summarized separately in **Section IX.E: Stability**.

Table IX.D-T1: CMC Release Testing

Test	Description of Test
Material Analysis – Polymer	The polymer is tested at incoming inspection to ensure conformity to specifications. The polymer 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 finished combination product.

Test	Description of Test
Drug Content/Content Uniformity	Multiple stents are assayed to verify the uniformity of the drug content between individual stents is within the specifications established for the finished combination product.
Impurities and Degradation Products	Testing is conducted to quantitatively verify the amount of impurities and degradation products in the finished product are within the specifications established for the finished combination product.
Drug Release	The <i>in vitro</i> drug release profile of everolimus is measured to verify that the drug release is within the specifications established for the finished combination product.
Particulates	Particulate counts are measured to verify that they remain below acceptable levels established for the finished combination product.
Residual Solvents	Testing is conducted to quantitatively verify the amount of N,N-Dimethylformamide and Tetrahydrofuran remain below acceptable levels established for the finished combination product.
BHT Content	Assay is conducted to verify the amount of butylated hydroxytoluene is within the specifications established for the finished combination product.
Molecular Weight and PDI	Assay to quantitatively verify the weight average molecular weight and Polydispersity Index of polymer in the drug constituent part.
Endotoxin	Testing is conducted to quantitatively verify endotoxin levels of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System are within the specifications established for the finished combination product.

E. Stability and Shelf Life

Stability studies were conducted to establish a shelf life for the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. The stability testing evaluation included appearance, drug content assay, impurities and degradants, drug release, particulates, sterility, butylated hydroxytoluene (BHT) content, molecular weight, polydispersity index, and endotoxin. Appropriate mechanical engineering tests were also performed on aged product and packaging to ensure that finished combination product continues to meet specification throughout its expiration dating. The data generated supports a shelf life of 12 months.

In addition, the stability of the drug substance has been independently verified. The PLGA polymer expiration date is supported by the vendor's drug master file.

F. Sterilization

The SYNERGY stent system (Monorail™ and Over-The-Wire) is sterilized using ethylene oxide sterilization and has been validated per AAMI/ISO 11135-1: 2007 "Sterilization of health care products – Ethylene Oxide—Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices."

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 for the finished combination product.

G. Animal Studies

Boston Scientific conducted multiple animal studies in the non-injured porcine model to assess the safety, vascular compatibility, and acute performance of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. These nonclinical animal tests assessed the comparability between SYNERGY, PROMUS Element, polymer only coated SYNERGY stents, and bare metal stents (OMEGA and SYNERGY). The results of these tests demonstrated acceptable safety and vascular compatibility of the SYNERGY stent in single and overlap-stent implant configurations in the non-injured porcine coronary artery. In addition, comparable results were obtained for early and late in-stent healing. The endothelial response of the SYNERGY stent was comparable to that observed in a bare metal stent at 90 days.

Similar *in vitro* and *in vivo* drug release profiles and local arterial tissue concentration profiles) were demonstrated through the nonclinical pharmacokinetic study. Furthermore, fast and slow drug release formulations of SYNERGY™ were evaluated 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 SYNERGY product. Summaries of all animal studies are included in **Table IX.G-T1**. Studies were conducted in accordance with §21 CFR 58 (Good Laboratory Practices).

Table IX.G-T1: Summary of the Major Supportive Animal Studies

Study Number	Stent Design	Drug Loading Density (µg/cm ²) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
GLP Safety Overlap Study 11-009G	SYNERGY 3.00 x 8 mm 3.50 x 8 mm (40 Single, 16 overlap pairs, 3 SEM)	1 / 45:55	Swine, 90	RCA, LAD, and/or LCX	5,28, 60, 90, 120, 180, 270 Days	Demonstrated safety. No device related mortality or morbidity. Vascular response showed early and late healing, vessel stability and patency over 5, 28, 60, 90, 120, 180, and 270 days.
GLP: Yes	SYNERGY 3x Polymer Only 3.00 x 8 mm 3.50 x 8 mm (55 single)	N/A/171 PLGA only				

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
	SYNERGY 1x Polymer Only 3.00 x 8 mm 3.50 x 8 mm (56 single, 17 overlap pairs, 3 SEM pairs)	N/A/57 PLGA only				
	Bare Metal SYNERGY 3.00 x 8 mm 3.50 x 8 mm (17 Single)	N/A				
	Bare Metal OMEGA 3.00 x 8 mm 3.50 x 8 mm (56 Single, 16 overlap pairs)	N/A				
Endothelial Cell Study 13-100G GLP: Yes	SYNERGY 3.00 X 8 mm 3.50 X 8 mm (13)	1 / 45:55	Swine, 9	RCA, LAD, and/or LCX	90 days	The presence and relative function of the endothelial cells, as determined by SEM and IHC in SYNERGY drug-eluting stents was comparable to Bare Metal Stent (OMEGA) response, with no discernable differences between groups.
	Bare Metal OMEGA 3.00 X 8 mm 3.00 X 8 mm (13)	N/A- Bare Stent				
Long Stent Safety Study 11-052G GLP: Yes	SYNERGY 3.00 x 20 mm 3.50 x 20 mm (26, 3 SEM)	1 / 45:55	Swine,28	RCA, LAD, and/or LCX	28, 90, and 180 days	Demonstrated safety. No device related mortality or morbidity. Vascular response showed early and late healing, vessel stability and patency over 28, 90, and 180 days.
	Bare Metal OMEGA 3.00 x 20 mm 3.50 x 20 mm (24, 3 SEM)	N/A – Bare Stent				

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
	PROMUS Element 3.00 x 20 mm 3.50 x 20 mm (26, 3 SEM)	1 / 16:84				
Safety Study 09-006N GLP: Yes	High Dose Element (PROMUS Dose) 3.00 x 12 mm 3.50 x 12 mm (46, 6 SEM)	1 / 45:55	Swine, 14	RCA, LAD, and/or LCX	30,90, 180, and 360 days	Demonstrated safety. No device related mortality or morbidity. Vascular response showed early and late healing, vessel stability and patency over 30, 90, 180, and 360 days.
	Low Dose Element (1/2 PROMUS Dose) 3.00 x 12 mm 3.50 x 12 mm (29, 7 SEM)	1 / 45:55				
	Polymer Only Element 3.00 x 12 mm 3.50 x 12 mm (31, 5 SEM)	N/A – PLGA Polymer Only				
	Bare Metal Element + Plasma Treatment 3.00 x 12 mm 3.50 x 12 mm (11, 4 SEM)	N/A- Bare Stent				
	Bare Metal Element 3.00 x 12 mm 3.50 x 12 mm (28, 4 SEM)	N/A- Bare Stent				
	PROMUS (XIENCE V) 3.00 x 12 mm 3.50 x 12 mm (31, 6 SEM)	1 / 16:84				

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
Pharmacokinetic (PK) Study 11-019G GLP: Yes	SYNERGY Maple Grove 3.00 x 8 mm 3.50 x 8 mm (100)	1 / 45:55	Swine, 134	RCA, LAD, RCA LAD, and/or LCX	3h, 6h, 1,3,7,14,28, 45,60,90, and 120 days	Comparable <i>in vivo</i> performance between SYNERGY FHU, MG, GAL stents supported by <i>in vivo</i> drug release profiles and arterial tissue concentration. PK analysis of arterial tissue concentrations shows all test devices have similar C _{max} and total drug exposure as quantified by AUC. Blood, myocardium, and distal organ everolimus concentrations all are low
	SYNERGY Galway 3.00 x 8 mm 3.50 x 8 mm (105)	1 / 45:55				
	SYNERGY FHU 3.00 x 8 mm 3.50 x 8 mm (102)	1 / 45:55				
Max Dose Study R051503-DMH (Histology) GLP: Yes	PROMUS (XIENCE V) 3.00 x 12 mm (11 histology, 1 SEM)	100 / 1:4.9	Swine, 14	RCA LAD, and/or LCX	180 days	Met angiographic criteria. Met vascular response safety criteria for both max dose and bulk polymer systems
	Vision Bare (Polymer Only) 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				
	Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w)^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
Max Dose Study R050503-DMH (Histology) GLP: Yes	PROMUS (XIENCE V) 3.00 x12 mm (11 histology, 1 SEM)	100 / 1:4.9	Swine,14	RCA LAD, and/or LCX	90 days	Met angiographic criteria. Met vascular response safety criteria for both max dose and bulk polymer systems
	Vision Bare (Polymer Only) 3.00 x 12 mm (11 histology, 1 SEM)	N/A /89 – Polymer Only				
	Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				
Max Dose Study R032204-PDD (Histology) GLP: Yes	PROMUS (XIENCE V) 3.00 x12 mm (11 histology, 1 SEM)	100 / 1:4.9	Swine, 13	RCA, LAD, and/or LCX	120 days	Met angiographic criteria. Met vascular response safety criteria for both max dose and bulk polymer systems
	Vision Bare (Polymer Only) 3.00 x 12 mm (11 histology, 1 SEM)	N/A/89 – Polymer Only				
	Vision Bare 3.00 x 12 mm (11 histology, 1 SEM)	N/A – Bare stent				

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
<p><i>In Vivo/In Vitro</i> Correlation Study 13-005G</p> <p>GLP: Yes</p>	<p>SYNERGY (Nominal Release)</p> <p>3.00 x 8 mm</p> <p>3.50 x 8 mm</p> <p>(102 stents tissue and 18 stents coating integrity)</p>	1 / 45:55	Swine, 71	RCA, LAD, and/or LCX	3, 6 hours, 1, 3, 7, 14, 28, 45, 60, 90, and 120 days	<p>The average everolimus remaining on the three formulations was essentially 0% at 120 days. The regional stented arterial concentration of everolimus tended to decrease from the 3 hour survival time point through 1 to 7 days for nominal and low formulations, and decreased from the 3 hour through 1 day for the fast formulation. All formulations increased again through 28 days, and then steadily diminished through 120 days.</p>
	<p>SYNERGY (Fast Release)</p> <p>3.00 x 8 mm</p> <p>3.50 x 8 mm</p> <p>(67 total stents)</p>	1 / 50:50				
	<p>PROMUS Element (Slow Release)</p> <p>3.00 x 8 mm</p> <p>3.50 x 8 mm</p> <p>(66 total stents)</p>	1 / 37.5:62.5				
<p>SYNERGY Acute Performance Study 13-163G</p> <p>GLP: Yes</p>	<p>SYNERGY</p> <p>2.25 x 16 mm</p> <p>2.50 x 16 mm</p> <p>2.75 x 16 mm</p> <p>3.00 x 16 mm</p> <p>3.50 x 16 mm</p> <p>4.00 x 16 mm</p> <p>(19)</p>	1 / 45:55	Swine, 3	RCA, LAD, and/or LCX	0.25, 1, 3, 7, 14, 28, 60 days	<p>All acute performance criteria for the SYNERGY stent and stent delivery system were rated Acceptable</p>

Study Number	Stent Design	Drug Loading Density ($\mu\text{g}/\text{cm}^2$) / (Drug: Polymer w/w) ^a	Type/ No. of Animals	Vessel Location	Evaluation Time Points	Results
Acute Performance Study 11-175G GLP: Yes	SYNERGY 2.25 x 16 mm 2.50 x 16 mm 2.75 x 16 mm 3.00 x 16 mm 3.50 x 16 mm 4.00 x 16 mm (16)	1 / 45:55	Swine, 2	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	All acute performance criteria for the SYNERGY stent and stent delivery system with Bioslide coating were rated Acceptable or higher.

H. In Vivo Pharmacokinetics

The pharmacokinetics (PK) of Everolimus released from the SYNERGY™ 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 EVOLVE II clinical trial. The design of the sub-study is described in **Section X: Summary of Clinical Studies**. Whole blood everolimus PK parameters are provided in **Table IX.H-T1** for groups with 3 or more patients receiving the SYNERGY™ stent.

Table IX.H-T1: Whole Blood Everolimus Pharmacokinetic Parameters (Mean \pm SD) for EVOLVE II Groups with Three or More Patients Following SYNERGY Stent Implantation

Region	USA*	Japan*	Combined		
Dose (μg)	NA	NA	58 μg ^b	113 μg ^c	189 μg
n			3 ^c	3 ^b	4 ^b
t _{max} : (h)			0.90 \pm 0.36	0.48 \pm 0.08	0.48 \pm 0.03
C _{max} : (ng/mL)			0.31 \pm 0.07	0.35 \pm 0.04	0.84 \pm 0.41
AUC _{0-t} : (ng.h/mL)			0.32 \pm 0.25	0.56 \pm 0.47	8.50 \pm 3.91
AUC _{0-24h} : (ng.h/mL)			0.32 \pm 0.25	0.56 \pm 0.47	6.73 \pm 2.10
AUC _{0-∞} : ^a (ng.h/mL)			NA	NA	47.81 \pm 61.50

Region	USA*	Japan*	Combined		
$t_{1/2}$: ^a (h)			NA	NA	105.79 ± 149.33
CL: ^a (L/h)			NA	NA	0.0545 ± 0.0436

Data are presented as n or mean ±SD

Abbreviation: NA=not assessable

*: Do not meet requirement of 3 or more subjects at any 1 dose level

a: Accurate determination not possible

b: n=0 for AUC_{0-∞}, $t_{1/2term}$ and CL

c: n=1 for AUC_{0-∞}, $t_{1/2term}$ 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-∞}= 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 1.18 hours. Individual C_{max} values ranged from 0.26 to 1.35 ng/mL. AUC_{0-24h} values ranged from 0.069 to 11.22 ng•h/mL, while AUC_{0-t} values ranged from 0.07 to 19.42 ng•h/mL. The concentration of everolimus was below the limit of quantification in all patients except 3 at 48 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, $t_{1/2}$ and AUC_{0-∞} could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents. Everolimus disappearance from circulation following SYNERGY 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.

H1. SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent

Boston Scientific Corporation has provided a letter from the drug substance manufacturer authorizing use of drug substance information in support of this application. *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 active pharmaceutical ingredient of SYNERGY is identical to that of the PROMUS (XIENCE® V) Everolimus Eluting Coronary Stent System, the evaluation of PROMUS (XIENCE® V) is applicable to SYNERGY.

H2. 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™ Plus 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™ Plus 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 (ketaconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential reaction)
- Sildenafil (Viagra®) (theoretical potential reaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

X. SUMMARY OF CLINICAL STUDIES

The EVOLVE II Clinical Program evaluates the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of atherosclerotic lesions in 3 studies. The Program includes the EVOLVE II trial, (randomized controlled trial (RCT) with a parallel single-arm pharmacokinetics (PK) sub-study, and consecutive single arm diabetic (DM) sub-study). Additionally, EVOLVE II QCA, a quantitative coronary angiography (QCA) study was conducted. A summary of the RCT, PK, diabetic, and QCA trial designs is presented in **Table X-T1**.

Additionally NG PROMUS data is presented in **Table X.E4-T1** to support the minor stent design changes that took place to the SYNERGY stent platform after the EVOLVE II trial was underway. The design changes assessed in the NG PROMUS trial are comparable to those incorporated in the final SYNERGY design. A summary of the NG PROMUS trial design is presented in **Section E**.

Table X-T1: Comparison of EVOLVE II Clinical Studies

	EVOLVE II			EVOLVE II QCA
	RCT	PK	Diabetic	
Purpose	Evaluation of safety and effectiveness in native coronary lesions	Evaluation of everolimus blood levels	Evaluation of safety and effectiveness in native coronary lesions in patients with medically treated diabetes mellitus	Evaluation of angiographic and IVUS outcomes in native coronary lesions
Study Design	Prospective, randomized, controlled, multicenter, single-blind non-inferiority to PROMUS Element Plus	Prospective, single arm, multicenter, observational study	Prospective, single arm, multicenter, comparison to performance goal	Prospective, single arm, multicenter, observational; study
Primary Endpoint	12M TLF	N/A, observational	12M TLF	9 month in-stent late loss
Number of Patients (ITT)	1684 enrolled; SYNERGY: 846 PROMUS Element Plus: 838	21 SYNERGY	203 SYNERGY	100 SYNERGY
Polymer	PLGA			
Everolimus Dose Density	58 to 257 µg			
Lesion Criteria: Vessel Diameter (by visual estimate), mm	≥2.25to ≤4.00			
Lesion Criteria: Lesion Length (by visual estimate), mm	≤34			
Total Target Lesions	Up to 3 in 2 epicardial vessels			

	EVOLVE II			EVOLVE II QCA
	RCT	PK	Diabetic	
Stent Matrix Diameter	Diameter: 2.25, 2.50, 3.00, 3.50, 4.00 Length: 8, 12, 20, 28, 32/38*			
Post-Procedure Antiplatelet Therapy	A P2Y12 inhibitor for at least 6 months, ideally for 12 months in patients who were 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; Angiographic: 9 month; IVUS: 9 month

Abbreviations: ASA=aspirin; IVUS=intravascular ultrasound; PK=pharmacokinetics; QCA=quantitative coronary angiography; RCT=randomized controlled trial; TLF=target lesion failure

A. EVOLVE II Pivotal Clinical Trial

A1. Study Design

The EVOLVE II RCT is a prospective, randomized (1:1), controlled, single-blind, multicenter, non-inferiority trial designed to evaluate the safety and effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System compared to the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of native coronary lesions. Patients with a maximum of 3 lesions in 2 epicardial vessels ≤ 34 mm in length (visual estimate) in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm (visual estimate) in diameter were considered for enrollment.

Clinical Inclusion and Exclusion Criteria

Table X.A1-T1: EVOLVE II Clinical Inclusion and Exclusion Criteria

Clinical Inclusion Criteria	<p>CI1. Subject must be at least 18 years of age</p> <p>CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed</p> <p>CI3. For subjects less than 20 years of age enrolled at a Japanese site, the subject and the subject's legal representative must provide written informed consent before any study-specific tests or procedures are performed</p> <p>CI4. Subject is eligible for percutaneous coronary intervention (PCI)</p> <p>CI5. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia</p> <p>CI6. Subject is an acceptable candidate for coronary artery bypass grafting (CABG)</p> <p>CI7. Subject is willing to comply with all protocol-required follow-up evaluation</p>
Angiographic Inclusion Criteria (visual estimate)	<p>AI1. Target lesion(s) must be located in a native coronary artery with a visually estimated reference vessel diameter (RVD) ≥ 2.25 mm and ≤ 4.0 mm</p> <p>AI2. Target lesion(s) length must be ≤ 34 mm (by visual estimate)</p> <p>AI3. Target lesion(s) must have visually estimated stenosis $\geq 50\%$ and $< 100\%$ with thrombolysis in Myocardial Infarction (TIMI) flow > 1 and one of the following: stenosis $\geq 70\%$, abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure</p> <p>AI4. Coronary anatomy is likely to allow delivery of a study device to the target lesions(s)</p> <p>AI5. The first lesion treated must be successfully predilated/pretreated</p> <p><i>Note:</i> Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C.</p>

Clinical Exclusion Criteria	<p>CE1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI)</p> <p>CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina</p> <p>CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant</p> <p>CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure</p> <p>CE5. Planned PCI (including staged procedures) or CABG after the index procedure</p> <p>CE6. Subject previously treated at any time with intravascular brachytherapy</p> <p>CE7. Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel, everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors, or aspirin)</p> <p>CE8. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"> ○ Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 24 months ○ Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) ○ Planned procedure that may cause non-compliance with the protocol or confound data interpretation <p>CE9. Subject is receiving chronic (≥ 72 hours) anticoagulation therapy (i.e., heparin, coumadin) for indications other than acute coronary syndrome</p> <p>CE10. Subject has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³</p> <p>CE11. Subject has a white blood cell (WBC) count $< 3,000$ cells/mm³</p> <p>CE12. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis</p> <p>CE13. Subject is on dialysis or has baseline serum creatinine level > 2.0 mg/dL (177μmol/L)</p> <p>CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions</p> <p>CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months</p> <p>CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding</p> <p>CE17. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) at the time of the index procedure</p> <p>CE18. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint</p> <p>CE19. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure</p> <p>CE20. Subject 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)</p> <p>CE21. Subject 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)</p>
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Angiographic Exclusion Criteria (visual estimate)	<p>AE1. Planned treatment of more than 3 lesions</p> <p>AE2. Planned treatment of lesions in more than 2 major epicardial vessels</p> <p>AE3. Planned treatment of a single lesion with more than 1 stent</p> <p><i>Note:</i> Planned use of 2 overlapping stents will be allowed in subjects randomized to PROMUS Element Plus where lesion length is ≥ 28 mm and 2.25 mm stents are used.</p> <p>AE4. Subject has 2 target lesions in the same vessel that are separated by less than 15 mm (by visual estimate)</p> <p>AE5. Target lesion(s) is located in the left main</p> <p>AE6. Target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate</p> <p>AE7. Target lesion(s) is located within a saphenous vein graft or an arterial graft</p> <p>AE8. Target lesion(s) will be accessed via a saphenous vein graft or arterial graft</p> <p>AE9. Target lesion(s) with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing</p> <p>AE10. Target lesion(s) treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent)</p> <p>AE11. Target lesion(s) is restenotic from a previous stent implantation or study stent would overlap with a previous stent</p> <p>AE12. Subject has unprotected left main coronary artery disease ($>50\%$ diameter stenosis)</p> <p>AE13. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon atherectomy) within 24 hours prior to the index procedure</p> <p>AE14. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)</p>
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Follow-up Schedule

Clinical follow-up was required at the following time points for the RCT: in hospital, 30 days, 6 months, 12 months, 18 months and then annually between 2 and 5 years after the index procedure. Subjects who were enrolled but who did not receive a study stent will be followed through 12 months only. Starting with the 18 month follow-up, only the Safety Population (i.e., those subjects who receive a study stent) will be followed.

The study is now considered complete with regard to the 12-month primary endpoint. Additional follow-up is ongoing to 5 years.

Clinical Endpoints

The primary endpoint was the rate of 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, at 12 months post-index procedure. EVOLVE II RCT was designed to test the hypothesis that the rate of 12-month TLF in patients treated with the SYNERGY is non-inferior to the rate of 12-month TLF in patients treated with the PROMUS Element Plus.

Additional Endpoints

Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months, 18 months, 2 years, 3 years, 4 years, and 5 years in the RCT are:

- TLR rate
- TLF rate (primary endpoint at 12 months for the RCT)
- TVR rate
- All revascularization rate
- Target vessel failure (TVF) rate
- 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 rates (by Academic Research Consortium [ARC] definitions)
- Stroke rate (ischemic and hemorrhagic)
- Longitudinal stent deformation rate assessed by an independent angiographic core laboratory

Peri-procedural endpoints:

- Technical success rate
- Clinical procedural success rate
- Longitudinal stent deformation assessed by an independent angiographic core laboratory

A2. Accountability of PMA Cohort: EVOLVE II RCT Study

A total of 1684 patients (846 SYNERGY and 838 PROMUS Element Plus) were randomized at 125 centers in the United States (US), Canada, Europe, Australia, New Zealand, Japan and Singapore from November 26, 2012 to August 29, 2013 (GMT -4). Of the 1,684 patients included in the intent-to-treat analysis set, a total of 1630 patients (826 SYNERGY and 804 PROMUS Element Plus) were evaluable for the 12 month primary endpoint.

Table X.A2-T1: EVOLVE II RCT Subject Disposition, ITT Analysis Set

	PROMUS Element Plus	SYNERGY	Total
Intent-to-Treat Analysis Set	838	846	1684
Death ≤395 days with no 12-Month Clinical Follow-up Performed	9	9	18
Eligible for 12-Month Clinical Follow-up^a	829	837	1666
12-Month Clinical Follow-up Performed^b	96.1% (797/829)	98.2% (822/837)	97.2% (1619/1666)

No 12-Month Clinical Follow-up Performed	32	15	47
Prematurely Discontinued	9	7	16
Death > 395 days	0	0	0
Withdrew Consent	3	5	8
Lost to Follow-up	0	0	0
Adverse Event	0	0	0
Investigator Discretion	6	2	8
Other	0	0	0
Missed 12-Month Visit	23	8	31
With Later Follow-up Visit Performed	0	0	0
No Later Follow-up Visit Performed	23	8	31
12-Month Clinical Follow-up or Death^c	96.2% (806/838)	98.2% (831/846)	97.2% (1637/1684)
12-Month Clinical Follow-up Subject Accountability^d	95.1% (797/838)	97.2% (822/846)	96.1% (1619/1684)

Numbers are n or % (count/sample size).

a: Subjects who died prior to completion of the follow-up window and prior to completing a 12-month clinical follow-up visit were considered censored and were excluded from calculation of proportion of subjects who completed clinical follow-up visit.

b: Based on subjects eligible for 12-month clinical follow-up (excludes subjects who died within 395 days with no 12-month follow-up).

c: Includes subjects who have died in both the numerator and the denominator; based on the Intent-to-Treat analysis set.

d: Includes subjects who have died in the denominator only; based on the Intent-to-Treat analysis set.

A3. Study Population Demographics and Baseline Parameters

Table X.A3-T1 and **Table X.A3-T2** present demographics and baseline clinical characteristics for the ITT analysis set (N=846 SYNERGY and N=838 PROMUS Element Plus (Control)). The ITT population was predominantly male (70.6%/72.7%) with a history of medically treated hyperlipidemia (74%/74.5%) and hypertension (77.3%/75.1%). Medically treated diabetic subjects accounted for 31.1%/30.8% of ITT subjects. Unstable angina was reported for 33.9%/34.8% of subjects and 25.9%/29.2% had a history of MI.

Table X.A3-T1: Baseline Demographic and Clinical Characteristics, ITT Analysis Set

Variable	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	Difference [95% CI]	P value^a
Male	72.7% (609/838)	70.6% (597/846)	-2.1% [-6.4%, 2.2%]	0.3379
Age (yr)	63.92±10.50 (838) (32, 93)	63.48±10.44 (846) (26, 88)	-0.43 [-1.43, 0.57]	0.3975
Ethnicity and Race ^b				
American Indian or Alaska native	0.2% (2/838)	0.1% (1/846)	-0.1% [NA]	0.6230*
Asian	11.9% (100/838)	11.8% (100/846)	-0.1% [-3.2%, 3.0%]	0.9429
Japanese	9.9% (83/838)	8.7% (74/846)	-1.2% [-3.9%, 1.6%]	0.4140
Chinese	1.3% (11/838)	2.0% (17/846)	0.7% [-0.5%, 1.9%]	0.2635
Korean	0.0% (0/838)	0.0% (0/846)	0.0% [NA, NA]	Undef
Other Asian	0.7% (6/838)	1.1% (9/846)	0.3% [-0.5%, 1.2%]	0.4475

Variable	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	Difference [95% CI]	P value^a
Black, of African heritage	4.4% (37/838)	6.1% (52/846)	1.7% [-0.4%, 3.9%]	0.1123
Caucasian	79.2% (664/838)	77.4% (655/846)	-1.8% [-5.7%, 2.1%]	0.3666
Hispanic or Latino	1.9% (16/838)	1.8% (15/846)	-0.1% [-1.4%, 1.1%]	0.8352
Native Hawaiian or other Pacific Islander	0.2% (2/838)	0.4% (3/846)	0.1% [NA]	1.0000*
Other	0.6% (5/838)	0.5% (4/846)	-0.1% [NA]	0.7522*
Not Disclosed	1.6% (13/838)	2.4% (20/846)	0.8% [-0.5%, 2.1%]	0.2289
Physical Assessment				
Height (ins)	67.44±4.07 (837) (53, 84)	67.23±4.00 (845) (54, 77)	-0.22 [-0.60, 0.17]	0.2687
Weight (lbs)	190.45±44.29 (838) (82, 368)	190.92±44.09 (846) (84, 400)	0.46 [-3.76, 4.69]	0.8293
General Medical History				
Smoking, Ever	62.8% (519/826)	61.7% (510/827)	-1.2% [-5.8%, 3.5%]	0.6254
Current	22.4% (185/826)	21.8% (180/827)	-0.6% [-4.6%, 3.4%]	0.7569
Previous	40.4% (334/826)	39.9% (330/827)	-0.5% [-5.3%, 4.2%]	0.8252
Smoking, Unknown	1.4% (12/838)	2.2% (19/846)	0.8% [-0.5%, 2.1%]	0.2141
Current Diabetes Mellitus	32.9% (276/838)	32.5% (275/846)	-0.4% [-4.9%, 4.1%]	0.8510

Variable	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	Difference [95% CI]	P value ^a
Current Method of Treatment				
Diet (only)	2.1% (18/838)	1.4% (12/846)	-0.7% [-2.0%, 0.5%]	0.2578
Medically-treated	30.8% (258/838)	31.1% (263/846)	0.3% [-4.1%, 4.7%]	0.8941
Oral Agent	25.9% (217/838)	25.5% (216/846)	-0.4% [-4.5%, 3.8%]	0.8647
Insulin	10.9% (91/838)	12.3% (104/846)	1.4% [-1.6%, 4.5%]	0.3578
Injectable agent (other than insulin)	0.4% (3/838)	0.1% (1/846)	-0.2% [NA]	0.3722*
Unknown	0.0% (0/838)	0.0% (0/846)	0.0% [NA, NA]	Undef
Hyperlipidemia Requiring Medication	74.5% (621/834)	74.0% (625/845)	-0.5% [-4.7%, 3.7%]	0.8163
Hypertension Requiring Medication	75.1% (629/837)	77.3% (652/843)	2.2% [-1.9%, 6.3%]	0.2908
History of bleeding disorder	0.1% (1/835)	0.2% (2/841)	0.1% [NA]	1.0000*
History of GI Bleeding	0.0% (0/835)	0.2% (2/841)	0.2% [NA]	0.4997*
Comorbidities				
History of TIA	2.7% (23/838)	2.9% (24/841)	0.1% [-1.5%, 1.7%]	0.8922
History of CVA	3.8% (32/838)	3.6% (30/842)	-0.3% [-2.1%, 1.5%]	0.7811
History of TIA or CVA	5.8% (49/838)	5.7% (48/839)	-0.1% [-2.4%, 2.1%]	0.9119
History of PVD	7.1% (59/836)	8.1% (68/840)	1.0% [-1.5%, 3.6%]	0.4221
History of Renal Disease	6.2% (52/838)	6.6% (56/844)	0.4% [-1.9%, 2.8%]	0.7192
Family History of CAD	58.1% (438/754)	58.5% (459/784)	0.5% [-4.5%, 5.4%]	0.8562
History of PCI	37.3% (312/836)	35.8% (303/846)	-1.5% [-6.1%, 3.1%]	0.5217
History of CABG	6.1% (51/838)	4.6% (39/846)	-1.5% [-3.6%, 0.7%]	0.1782
History of Myocardial Infarction	24.3% (202/832)	21.2% (179/846)	-3.1% [-7.1%, 0.9%]	0.1271
History of Congestive Heart Failure	9.0% (75/837)	8.3% (70/844)	-0.7% [-3.4%, 2.0%]	0.6264
NYHA Classification				
I	2.4% (20/837)	3.3% (28/844)	0.9% [-0.7%, 2.5%]	0.2533
II	3.6% (30/837)	3.1% (26/844)	-0.5% [-2.2%, 1.2%]	0.5651
III	2.3% (19/837)	1.3% (11/844)	-1.0% [-2.2%, 0.3%]	0.1344
IV	0.0% (0/837)	0.0% (0/844)	0.0% [NA, NA]	Undef
Unknown	0.7% (6/837)	0.6% (5/844)	-0.1% [-0.9%, 0.6%]	0.7517
History of Arrhythmia	7.8% (65/835)	7.5% (63/844)	-0.3% [-2.9%, 2.2%]	0.8049
History of Atrial Fibrillation	3.0% (25/834)	4.5% (38/845)	1.5% [-0.3%, 3.3%]	0.1060
Current Anginal Status				
Stable Angina	52.3% (438/838)	54.0% (457/846)	1.8% [-3.0%, 6.5%]	0.4714
CCS Classification				

Variable	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	Difference [95% CI]	P value ^a
1	10.6% (89/838)	11.5% (97/846)	0.8% [-2.1%, 3.8%]	0.5801
2	19.9% (167/838)	21.9% (185/846)	1.9% [-1.9%, 5.8%]	0.3278
3	17.9% (150/838)	18.1% (153/846)	0.2% [-3.5%, 3.9%]	0.9211
4	2.6% (22/838)	1.5% (13/846)	-1.1% [-2.5%, 0.3%]	0.1174
Unknown	1.2% (10/838)	1.1% (9/846)	-0.1% [-1.1%, 0.9%]	0.8014
Unstable Angina	34.8% (292/838)	33.9% (287/846)	-0.9% [-5.5%, 3.6%]	0.6909
Braunwald Classification				
IA	0.8% (7/838)	0.8% (7/846)	0.0% [-0.9%, 0.9%]	0.9858
IB	6.1% (51/838)	5.7% (48/846)	-0.4% [-2.7%, 1.8%]	0.7192
IC	0.2% (2/838)	0.1% (1/846)	-0.1% [NA]	0.6230*
IIA	0.4% (3/838)	0.5% (4/846)	0.1% [NA]	1.0000*
IIB	7.6% (64/838)	8.2% (69/846)	0.5% [-2.1%, 3.1%]	0.6931
IIC	0.5% (4/838)	0.2% (2/846)	-0.2% [NA]	0.4502*
IIIA	1.8% (15/838)	1.3% (11/846)	-0.5% [-1.7%, 0.7%]	0.4151
IIIB	15.0% (126/838)	14.4% (122/846)	-0.6% [-4.0%, 2.8%]	0.7218
IIIC	0.4% (3/838)	0.5% (4/846)	0.1% [NA]	1.0000*
Unknown	2.0% (17/838)	2.2% (19/846)	0.2% [-1.2%, 1.6%]	0.7580
No Angina	12.9% (108/838)	12.1% (102/846)	-0.8% [-4.0%, 2.3%]	0.6058
Silent Ischemia	17.1% (127/741)	15.9% (121/759)	-1.2% [-5.0%, 2.6%]	0.5327
MI ^b	29.2% (245/838)	25.9% (219/846)	-3.3% [-7.6%, 0.9%]	0.1240
LVEF Measurement (%)	56.94±10.31 (648) (20.00, 88.00)	56.69±10.69 (646) (10.00, 85.00)	-0.25 [-1.39, 0.89]	0.6692
History of Multivessel Disease	33.5% (278/829)	31.4% (264/841)	-2.1% [-6.6%, 2.3%]	0.3496
History of Left Main Disease	2.6% (22/832)	2.5% (21/843)	-0.2% [-1.7%, 1.4%]	0.8429

Numbers are presented as % (count/sample size), or mean± standard deviation (n) (minimum, maximum).

a: P values are two-sided and from Student t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables.

b: The indication for the procedure was considered to be an MI if any of the following were met:

- 1) Site indicated in the CRF that the indication for the procedure was an MI, or
- 2) Subjects have positive pre-procedure CK-MB (>1URL), or
- 3) Subjects have positive pre-procedure Troponin (>1URL), or
- 4) Subjects have positive pre-procedure CK (>1URL) and both pre-procedure CK-MB and Troponin were not measured.

Abbreviation: ITT=intent-to-treat; CAD=coronary artery disease; MI=myocardial infarction; CHF=congestive heart failure; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery; LVEF= Left Ventricular Ejection Fraction; URL=upper reference limit.

Table X.A3-T2: Cardiac History, ITT Analysis Set

Parameter	PROMUS Element Plus (N=838 Subjects)	SYNERGY N=846 (Subjects)	Difference [95% CI]	P value ^a
Family History of CAD	58.1% (438/754)	58.5% (459/784)	0.5% [-4.5%, 5.4%]	0.8562
History of PCI	37.3% (312/836)	35.8% (303/846)	-1.5% [-6.1%, 3.1%]	0.5217
History of CABG	6.1% (51/838)	4.6% (39/846)	-1.5% [-3.6%, 0.7%]	0.1782

Parameter	PROMUS Element Plus (N=838 Subjects)	SYNERGY N=846 (Subjects)	Difference [95% CI]	P value ^a
History of Myocardial Infarction	24.3% (202/832)	21.2% (179/846)	-3.1% [-7.1%, 0.9%]	0.1271
History of Congestive Heart Failure	9.0% (75/837)	8.3% (70/844)	-0.7% [-3.4%, 2.0%]	0.6264
NYHA Classification				
I	2.4% (20/837)	3.3% (28/844)	0.9% [-0.7%, 2.5%]	0.2533
II	3.6% (30/837)	3.1% (26/844)	-0.5% [-2.2%, 1.2%]	0.5651
III	2.3% (19/837)	1.3% (11/844)	-1.0% [-2.2%, 0.3%]	0.1344
IV	0.0% (0/837)	0.0% (0/844)	0.0% [NA, NA]	Undef
Unknown	0.7% (6/837)	0.6% (5/844)	-0.1% [-0.9%, 0.6%]	0.7517
History of Arrhythmia	7.8% (65/835)	7.5% (63/844)	-0.3% [-2.9%, 2.2%]	0.8049
History of Atrial Fibrillation	3.0% (25/834)	4.5% (38/845)	1.5% [-0.3%, 3.3%]	0.1060
Current Anginal Status				
Stable Angina	52.3% (438/838)	54.0% (457/846)	1.8% [-3.0%, 6.5%]	0.4714
CCS Classification				
1	10.6% (89/838)	11.5% (97/846)	0.8% [-2.1%, 3.8%]	0.5801
2	19.9% (167/838)	21.9% (185/846)	1.9% [-1.9%, 5.8%]	0.3278
3	17.9% (150/838)	18.1% (153/846)	0.2% [-3.5%, 3.9%]	0.9211
4	2.6% (22/838)	1.5% (13/846)	-1.1% [-2.5%, 0.3%]	0.1174
Unknown	1.2% (10/838)	1.1% (9/846)	-0.1% [-1.1%, 0.9%]	0.8014
Unstable Angina	34.8% (292/838)	33.9% (287/846)	-0.9% [-5.5%, 3.6%]	0.6909
Braunwald Classification				
IA	0.8% (7/838)	0.8% (7/846)	0.0% [-0.9%, 0.9%]	0.9858
IB	6.1% (51/838)	5.7% (48/846)	-0.4% [-2.7%, 1.8%]	0.7192
IC	0.2% (2/838)	0.1% (1/846)	-0.1% [NA]	0.6230 *
IIA	0.4% (3/838)	0.5% (4/846)	0.1% [NA]	1.0000 *
IIB	7.6% (64/838)	8.2% (69/846)	0.5% [-2.1%, 3.1%]	0.6931
IIC	0.5% (4/838)	0.2% (2/846)	-0.2% [NA]	0.4502 *
IIIA	1.8% (15/838)	1.3% (11/846)	-0.5% [-1.7%, 0.7%]	0.4151
IIIB	15.0% (126/838)	14.4% (122/846)	-0.6% [-4.0%, 2.8%]	0.7218
IIIC	0.4% (3/838)	0.5% (4/846)	0.1% [NA]	1.0000 *
Unknown	2.0% (17/838)	2.2% (19/846)	0.2% [-1.2%, 1.6%]	0.7580
No Angina	12.9% (108/838)	12.1% (102/846)	-0.8% [-4.0%, 2.3%]	0.6058
Silent Ischemia	17.1% (127/741)	15.9% (121/759)	-1.2% [-5.0%, 2.6%]	0.5327

Parameter	PROMUS Element Plus (N=838 Subjects)	SYNERGY N=846 (Subjects)	Difference [95% CI]	P value ^a
MI ^b	29.2% (245/838)	25.9% (219/846)	-3.3% [-7.6%, 0.9%]	0.1240
LVEF Measurement (%)	56.94±10.31 (648) (20.00, 88.00)	56.69±10.69 (646) (10.00, 85.00)	-0.25 [-1.39, 0.89]	0.6692
History of Multivessel Disease	33.5% (278/829)	31.4% (264/841)	-2.1% [-6.6%, 2.3%]	0.3496
History of Left Main Disease	2.6% (22/832)	2.5% (21/843)	-0.2% [-1.7%, 1.4%]	0.8429

Numbers are presented as % (count/sample size), or mean± standard deviation (n) (minimum, maximum).

a: P values are two-sided and from Student t Test for continuous variables and the Chi-square or Fisher's Exact (*) Test for discrete variables.

b: The indication for the procedure was considered to be an MI if any of the following were met:

- 1) Site indicated in the CRF that the indication for the procedure was an MI, or
- 2) Subjects have positive pre-procedure CK-MB (>1URL), or
- 3) Subjects have positive pre-procedure Troponin (>1URL), or
- 4) Subjects have positive pre-procedure CK (>1URL) and both pre-procedure CK-MB and Troponin were not measured.

Abbreviation: ITT=intent-to-treat; CAD=coronary artery disease; MI=myocardial infarction; CHF=congestive heart failure; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery; LVEF= Left Ventricular Ejection Fraction; URL=upper reference limit;

A4. Safety and Effectiveness Results

Principal safety and effectiveness results of the RCT through 12 months are summarized below and in the table following. Subject flow is shown in the diagram following the table.

- For the primary endpoint analysis of 12-month rate of target lesion failure:
 - The ITT rate was observed in 6.5% of PROMUS Element Plus and 6.7% SYNERGY treated subjects (difference=0.2%; 97.5% upper confidence bound=2.68%; P=0.0005 for non-inferiority)
 - The per protocol rate was observed in 6.4% of PROMUS Element Plus and 6.4% SYNERGY treated subjects (difference=0.0%; 97.5% upper confidence bound=2.51%; P=0.0003 for non-inferiority)
 - There were 7 cardiac deaths in the PROMUS Element Plus arm (0.9%) and 4 in the SYNERGY arm (0.5%; P=0.34)
- A total of 40 PROMUS Element Plus subjects (5.0%) and 45 SYNERGY subjects (5.4%) had a myocardial infarction (P=0.68)
- Five subjects in the PROMUS Element arm (0.6%) and 3 subjects in the SYNERGY arm (0.4%) experienced definite or probable stent thrombosis through 12 months (P=0.50); definite/probable stent thrombosis was not observed beyond 6 days following SYNERGY implantation
- The technical success rate was 96.9% (1011/1043) and 98.3% (1041/1059) in PROMUS Element Plus and SYNERGY subjects, respectively (P=0.04)
- The clinical procedural success rate was 94.3% (790/838) in the PROMUS Element Plus arm and 94.9% (803/846) in the SYNERGY arm

Table X.A4-T1 Primary Endpoint Results

12-Month TLF	PROMUS Element Plus	SYNERGY	Difference [95% CI]	One-sided 97.5% UCB ^a	Delta ^b	1-Sided P value for non-inferiority ^c
Intent-to-Treat Subjects	(N=838)	(N=846)				
	6.5% (52/804)	6.7% (55/826)	0.2% [-2.2%, 2.6%]	2.68%	4.4%	0.0005
Per Protocol Subjects	(N=829)	(N=843)				
	6.4% (51/796)	6.4% (53/823)	0.0% [-2.4%, 2.4%]	2.51%	4.4%	0.0003

Numbers are % (count/sample size)

a: Farrington-Manning upper confidence bound

b: Non-inferiority margin

c: P value is from the Farrington-Manning test and is based on the standard normal distribution

Abbreviations: ITT=intent-to-treat; TLF=target lesion failure (including any ischemia-driven revascularization of the target lesion, myocardial infarction [Q-wave and non-Q-wave] related to the target vessel, or any cardiac death)

Table X.A4-T2: Principal Effectiveness and Safety Results, ITT Analysis Set (12 Months)

Events	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	P value
12-Month Clinical Endpoints			
All Death, MI, TVR	8.4% (68/808)	9.3% (77/832)	0.5496
All Death or MI	5.8% (47/808)	6.3% (52/832)	0.7127
All Death	1.1% (9/808)	1.1% (9/832)	0.9502
Cardiac Death	0.9% (7/808)	0.5% (4/832)	0.3389
Non-Cardiac Death	0.2% (2/808)	0.6% (5/832)	0.4525*
MI ^a	5.0% (40/808)	5.4% (45/832)	0.6756
Related to TV	4.7% (38/808)	4.3% (36/832)	0.7138
Not related to TV	0.2% (2/808)	1.1% (9/832)	0.0385
Q-wave MI	0.2% (2/808)	0.2% (2/832)	1.0000*
Related to TV	0.2% (2/808)	0.2% (2/832)	1.0000*
Not related to TV	0.0% (0/808)	0.0% (0/832)	Undef
Non-Q-wave MI	4.7% (38/808)	5.2% (43/832)	0.6637
Related to TV	4.5% (36/808)	4.1% (34/832)	0.7118
Not related to TV	0.2% (2/808)	1.1% (9/832)	0.0385
TVR, Overall	3.6% (29/808)	3.8% (32/832)	0.7833
TLR, Overall	1.7% (14/808)	2.6% (22/832)	0.2078
Non-TLR TVR, Overall	2.2% (18/808)	1.8% (15/832)	0.5402
Cardiac Death or MI	5.6% (45/808)	5.6% (47/832)	0.9441
TLF	6.4% (52/808)	6.6% (55/832)	0.8860
TVF	8.2% (66/808)	8.2% (68/832)	0.9972
ARC Stent Thrombosis	0.7% (6/808)	0.6% (5/832)	0.7706*
Definite or Probable	0.6% (5/808)	0.4% (3/832)	0.5008*
Definite	0.2% (2/808)	0.2% (2/832)	1.0000*
Probable	0.4% (3/808)	0.1% (1/832)	0.3674
Possible	0.1% (1/808)	0.2% (2/832)	1.0000*
Stroke	0.9% (7/808)	0.7% (6/832)	0.7403
Ischemic Stroke	0.9% (7/808)	0.6% (5/832)	0.5284

Events	PROMUS Element Plus (N=838 Subjects)	SYNERGY (N=846 Subjects)	P value
12-Month Clinical Endpoints			
Hemorrhagic Stroke	0.0% (0/808)	0.0% (0/832)	Undef
Undetermined Stroke	0.0% (0/808)	0.1% (1/832)	1.0000*
Longitudinal Stent Deformation	0.1% (1/1079)	0.1% (1/1111) ^b	1.0000*
Periprocedural Endpoints			
Procedural Success	94.3% (790/838)	94.9% (803/846)	0.5582
Technical Success	96.9% (1011/1043)	98.3% (1041/1059)	0.0396

Numbers are % (counts/sample size); P values are two-sided and from the chi-square or Fisher exact test (denoted with *). Clinical endpoints and procedure success are subject-based. Technical success is lesion-based. Longitudinal stent deformation is angiographic stent-based.

a: Spontaneous MI: rise and/or fall of cardiac biomarkers with ≥ 1 value >99 th percentile of the URL + evidence of myocardial ischemia. Peri-PCI MI: ≥ 1 of the following: i) CK-MB $>3X$ URL within 48 hours, ii) new pathological Q waves, iii) autopsy evidence.

b: Occurred in a PROMUS Element Plus stent used in a SYNERGY patient

Abbreviations: CI=confidence interval; ITT=intent-to-treat; NA=not applicable; TLF=target lesion failure (including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave

and non-Q-wave] related to the target vessel, or any cardiac death); TV=target vessel; TVF=target vessel failure (any ischemia-driven revascularization of the target vessel [TVR], MI related to the target vessel, or any cardiac death); Undef=undefined.

Table X.A4-T3: Clinical Endpoints through 12-months by Medically-treated Diabetes Status, ITT Analysis Set

12-Month Clinical Endpoints	Non-medically Treated Diabetic Subjects		Medically Treated Diabetic Subjects	
	PROMUS Element Plus (N=580 Subjects)	SYNERGY (N=583 Subjects)	PROMUS Element Plus (N=258 Subjects)	SYNERGY (N=263 Subjects)
All Death, MI, TVR	8.9% (50/562)	7.5% (43/576)	7.3% (18/246)	13.3% (34/256)
All Death or MI	6.4% (36/562)	5.0% (29/576)	4.5% (11/246)	9.0% (23/256)
All Death	1.1% (6/562)	0.7% (4/576)	1.2% (3/246)	2.0% (5/256)
Cardiac Death	0.9% (5/562)	0.2% (1/576)	0.8% (2/246)	1.2% (3/256)
Non-Cardiac Death	0.2% (1/562)	0.5% (3/576)	0.4% (1/246)	0.8% (2/256)
MI	5.5% (31/562)	4.3% (25/576)	3.7% (9/246)	7.8% (20/256)
Related to TV	5.2% (29/562)	3.5% (20/576)	3.7% (9/246)	6.3% (16/256)
Unknown relationship	0.2% (1/562)	0.0% (0/576)	0.0% (0/246)	0.4% (1/256)
Not related to TV	0.4% (2/562)	0.9% (5/576)	0.0% (0/246)	1.6% (4/256)
Q-wave MI	0.2% (1/562)	0.3% (2/576)	0.4% (1/246)	0.0% (0/256)
Related to TV	0.2% (1/562)	0.3% (2/576)	0.4% (1/246)	0.0% (0/256)
Not related to TV	0.0% (0/562)	0.0% (0/576)	0.0% (0/246)	0.0% (0/256)
Non-Q-wave MI	5.3% (30/562)	4.0% (23/576)	3.3% (8/246)	7.8% (20/256)
Related to TV	5.0% (28/562)	3.1% (18/576)	3.3% (8/246)	6.3% (16/256)
Unknown relationship	0.2% (1/562)	0.0% (0/576)	0.0% (0/246)	0.4% (1/256)
Not related to TV	0.4% (2/562)	0.9% (5/576)	0.0% (0/246)	1.6% (4/256)
TVR, Overall	3.2% (18/562)	2.6% (15/576)	4.5% (11/246)	6.6% (17/256)
TLR, Overall	1.4% (8/562)	1.4% (8/576)	2.4% (6/246)	5.5% (14/256)
Non-TLR TVR, Overall	2.3% (13/562)	1.7% (10/576)	2.0% (5/246)	2.0% (5/256)
Cardiac Death or MI	6.2% (35/562)	4.5% (26/576)	4.1% (10/246)	8.2% (21/256)
TLF	6.9% (39/562)	5.0% (29/576)	5.3% (13/246)	10.2% (26/256)

TVF	8.5% (48/562)	6.6% (38/576)	7.3% (18/246)	11.7% (30/256)
ARC Stent Thrombosis	0.7% (4/562)	0.2% (1/576)	0.8% (2/246)	1.6% (4/256)
Definite or Probable	0.7% (4/562)	0.2% (1/576)	0.4% (1/246)	0.8% (2/256)
Definite	0.2% (1/562)	0.0% (0/576)	0.4% (1/246)	0.8% (2/256)
Probable	0.5% (3/562)	0.2% (1/576)	0.0% (0/246)	0.0% (0/256)
Possible	0.0% (0/562)	0.0% (0/576)	0.4% (1/246)	0.8% (2/256)
Stroke	0.9% (5/562)	0.3% (2/576)	0.8% (2/246)	1.6% (4/256)
Ischemic Stroke	0.9% (5/562)	0.2% (1/576)	0.8% (2/246)	1.6% (4/256)
Hemorrhagic Stroke	0.0% (0/562)	0.0% (0/576)	0.0% (0/246)	0.0% (0/256)
Undetermined Stroke	0.0% (0/562)	0.2% (1/576)	0.0% (0/246)	0.0% (0/256)
Longitudinal Stent Deformation	0.1% (1/744)	0.0% (0/768)	0.0% (0/335)	0.3% (1/343)

Numbers are % (count/sample size)

P values are 2-sided and from Student *t* Test for continuous variables and the Chi-square or Fisher's Exact Test for discrete variables

Abbreviation: CI=confidence interval; ITT=intent-to-treat; NA=not applicable; TLF=target lesion failure (including any ischemia-driven revascularization of the target lesion [TLR], myocardial infarction [MI; Q-wave and non-Q-wave] related to the target vessel, or any cardiac death); TV=target vessel; TVF=target vessel failure (any ischemia-driven revascularization of the target vessel [TVR], MI related to the target vessel, or any cardiac death); Undef=undefined.

B. EVOLVE II PK Sub-study

B1. Study Overview

The intent of the PK sub-study was to confirm that the PK parameters measured following implantation of the SYNERGY device were consistent with prior studies conducted with the PROMUS® Element Plus devices. Refer to **Section H - *In Vivo Pharmacokinetics***, for results.

C. EVOLVE II DM Sub-study

C1. Study Design

EVOLVE II DM is a consecutive, single-arm, diabetic sub-study of the EVOLVE II Trial designed to evaluate the safety and effectiveness of the SYNERGY stent for the treatment of native atherosclerotic lesion(s) in subjects with medically treated diabetes mellitus.

Clinical Inclusion and Exclusion Criteria

A complete list of inclusion and exclusion criteria are provided in Table X.A1-T1: for the EVOLVE II clinical studies.

Follow-up Schedule

Clinical follow-up was required at the following time points: in hospital, 30 days, 6 months, 12 months, 18 months and then annually between 2 and 5 years after the index procedure. The study is now considered complete with regard to the 12-month primary endpoint. Additional follow-up is ongoing to 5 years.

Clinical Endpoints

The primary endpoint for the DM sub-study is 12-month (365 days) 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.

C2. Accountability of EVOLVE DM Cohort

A total of 203 subjects were enrolled at 48 sites in Asia-Pacific region, Europe, Canada and the United States.

C3. Study Population Demographics and Baseline Parameters

Enrollment in the diabetes sub-study is now complete and all patients have completed the 12 month primary endpoint. Data regarding patient demographics and baseline parameters will be analyzed and pooled with diabetic data from the EVOLVE II RCT study to present a full overview of the diabetic population that was studied.

C4. Safety and Effectiveness Results

Enrollment in the DM sub-study is now complete and all patients have completed the 12-month primary endpoint. Once data analysis is completed it will be pooled with the medically treated diabetic patients from the SYNERGY arm of the EVOLVE II RCT study. The DM data from the SYNERGY arm of the EVOLVE II RCT study is provided in Table X.A4-T3 above.

D. EVOLVE II QCA

D1. Study Design

The EVOLVE II QCA trial is a prospective, single-arm, multicenter, observational study. Subjects received the SYNERGY stent for the treatment of atherosclerotic coronary artery lesions in native coronary vessels ≤ 34 mm in length and diameter ≥ 2.25 mm to ≤ 4.0 mm (both by visual estimate).

Clinical Inclusion and Exclusion Criteria

Table X.D1-T1: Clinical Inclusion and Exclusion Criteria EVOLVE II QCA

Clinical Inclusion Criteria	<p>CI1. Subject must be at least 18 years of age</p> <p>CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed</p> <p>CI3. For subjects less than 20 years of age enrolled at a Japanese site, the subject and the subject's legal representative must provide written informed consent before any study-specific tests or procedures are performed</p> <p>CI4. Subject is eligible for percutaneous coronary intervention (PCI)</p> <p>CI5. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia</p> <p>CI6. Subject is an acceptable candidate for coronary artery bypass grafting (CABG)</p> <p>CI7. Subject is willing to comply with all protocol-required follow-up evaluation</p>
Angiographic Inclusion Criteria (visual estimate)	<p>AI1. Target lesion(s) must be located in a native coronary artery with a visually estimated reference vessel diameter (RVD) ≥ 2.25 mm and ≤ 4.0 mm</p> <p>AI2. Target lesion(s) length must be ≤ 34 mm (by visual estimate)</p> <p>AI3. Target lesion(s) must have visually estimated stenosis $\geq 50\%$ and $< 100\%$ with thrombolysis in Myocardial Infarction (TIMI) flow > 1 and one of the following (stenosis $\geq 70\%$, abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure)</p> <p>AI4. Coronary anatomy is likely to allow delivery of a study device to the target lesions(s)</p> <p>AI5. The first lesion treated must be successfully pre-dilated/pretreated</p> <p>Note: Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C.</p>

Clinical Exclusion Criteria	<p>CE1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI)</p> <p>CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina</p> <p>CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant</p> <p>CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure</p> <p>CE5. Planned PCI (including staged procedures) or CABG after the index procedure</p> <p>CE6. Subject previously treated at any time with intravascular brachytherapy</p> <p>CE7. Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel, everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors, or aspirin)</p> <p>CE8. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"> ○ Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 24 months ○ Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) ○ Planned procedure that may cause non-compliance with the protocol or confound data interpretation <p>CE9. Subject is receiving chronic (≥ 72 hours) anticoagulation therapy (i.e., heparin, coumadin) for indications other than acute coronary syndrome</p> <p>CE10. Subject has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³</p> <p>CE11. Subject has a white blood cell (WBC) count $< 3,000$ cells/mm³</p> <p>CE12. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis</p> <p>CE13. Subject is on dialysis or has baseline serum creatinine level > 2.0 mg/dL (177μmol/L)</p> <p>CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions</p> <p>CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months</p> <p>CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding</p> <p>CE17. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) at the time of the index procedure</p> <p>CE18. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint</p> <p>CE19. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure</p> <p>CE20. Subject 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)</p> <p>CE21. Subject 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)</p>
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Angiographic Exclusion Criteria (visual estimate)	<p>AE1. Planned treatment of more than 3 lesions</p> <p>AE2. Planned treatment of lesions in more than 2 major epicardial vessels</p> <p>AE3. Planned treatment of a single lesion with more than 1 stent</p> <p>AE4. Subject has 2 target lesions in the same vessel that are separated by less than 15 mm (by visual estimate)</p> <p>AE5. Target lesion(s) is located in the left main</p> <p>AE6. Target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate.</p> <p>AE7. Target lesion(s) is located within a saphenous vein graft or an arterial graft</p> <p>AE8. Target lesion(s) will be accessed via a saphenous vein graft or arterial graft</p> <p>AE9. Target lesion(s) with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing</p> <p>AE10. Target lesion(s) treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent)</p> <p>AE11. Target lesion(s) is restenotic from a previous stent implantation or study stent would overlap with a previous stent</p> <p>AE12. Subject has unprotected left main coronary artery disease (>50% diameter stenosis)</p> <p>AE13. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon atherectomy) within 24 hours prior to the index procedure</p> <p>AE14. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)</p>
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Follow-up Schedule

Clinical follow-up was required in hospital and at 30 days, 9 and 12 months after the index procedure. All patients were required to undergo 9 month angiography and IVUS assessments. The study is now considered complete.

Clinical Endpoints

Primary endpoint:

The primary endpoint is in-stent late loss at 9 months post-procedure as measured by QCA.

Additional Clinical endpoints

- TLR rate
- TLF rate
- TVR rate
- All revascularization rate
- Target vessel failure (TVF) rate
- 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 rates (by ARC definitions)
- Stroke rate (ischemic and hemorrhagic) as assessed by an independent angiographic core laboratory

Peri-procedural endpoints:

- Technical success rate
- Clinical procedural success rate
- In-stent and in-segment percent diameter stenosis (%DS) measured by QCA
- In-stent and in-segment minimum lumen diameter (MLD) measured by QCA
- In-stent and in-segment acute gain measured by QCA
- Longitudinal stent deformation as assessed by an independent angiographic core laboratory

Angiographic endpoints measured by QCA at 9 months post-index procedure:

- In-stent and in-segment %DS
- In-segment late loss
- In-stent and in-segment binary restenosis rate
- In-stent and in-segment MLD
- Stent fracture rate
- Longitudinal stent deformation rate

IVUS endpoints measured at 9 months post-index procedure:

- Incomplete apposition
- Percent net volume obstruction
- Stent, vessel and lumen area volumes

D2. Accountability of EVOLVE QCA Cohort

A total of 100 subjects were enrolled at 12 sites in the Australia, New Zealand, Singapore and Japan from March 25, 2013 to October 15, 2013. Because all patients received a SYNERGY Stent, the ITT and per-protocol analysis sets were identical. All patients were evaluable for clinical follow-up at 9 months post-procedure and 95 underwent angiography and 90 underwent IVUS.

D3. Study Population Demographics and Baseline Parameters

Table X.D3-T1 and **Table X.D3-T2** present demographics and baseline clinical characteristics for the ITT analysis set (N=100). The ITT population was predominantly male (80%) with a history of medically-treated hyperlipidemia and hypertension (approximately 90% and 71%, respectively) and a family history of coronary artery disease (approximately 69%). Thirty-three (33) percent had previously undergone percutaneous coronary intervention and 18% had a history of MI. Medically-treated diabetic subjects accounted for 17% of ITT subjects.

Table X.D3-T1: Baseline Demographic and Clinical Characteristics

Parameter	SYNERGY (N=100 Subjects)	[95% CI]
Male	80.0% (80/100)	[70.8%, 87.3%]

Table X.D3-T1: Baseline Demographic and Clinical Characteristics

Parameter	SYNERGY (N=100 Subjects)	[95% CI]
Age (yr)	64.49±10.21 (100)	[62.49, 66.49]
Ethnicity and Race		
American Indian or Alaska native	0.0% (0/100)	[0.0%, 3.6%]
Asian	28.0% (28/100)	[19.5%, 37.9%]
Japanese	10.0% (10/100)	[4.9%, 17.6%]
Chinese	11.0% (11/100)	[5.6%, 18.8%]
Korean	0.0% (0/100)	[0.0%, 3.6%]
Other Asian	7.0% (7/100)	[2.9%, 13.9%]
Black, of African heritage	0.0% (0/100)	[0.0%, 3.6%]
Caucasian	70.0% (70/100)	[60.0%, 78.8%]
Hispanic or Latino	0.0% (0/100)	[0.0%, 3.6%]
Native Hawaiian or other Pacific Islander	0.0% (0/100)	[0.0%, 3.6%]
Other	2.0% (2/100)	[0.2%, 7.0%]
Not disclosed	0.0% (0/100)	[0.0%, 3.6%]
Physical Assessment		
Height (ins)	67.25±3.93 (100)	[66.48, 68.02]
Weight (lbs)	182.82±37.46	[175.48, 190.16]
General Medical History		
Smoking, Ever	53.0% (53/100)	[42.8%, 63.1%]
Current	13.0% (13/100)	[7.1%, 21.2%]
Previous	40.0% (40/100)	[30.3%, 50.3%]
Current Diabetes Mellitus	22.0% (22/100)	[14.3%, 31.4%]
Current Method of Treatment		
Diet (only)	5.0% (5/100)	[1.6%, 11.3%]
Medically Treated	17.0% (17/100)	[10.2%, 25.8%]
Oral Agent	16.0% (16/100)	[9.4%, 24.7%]
Insulin	3.0% (3/100)	[0.6%, 8.5%]
Injectable agent (other than insulin)	0.0% (0/100)	[0.0%, 3.6%]
Unknown	0.0% (0/100)	[0.0%, 3.6%]
Hyperlipidemia Requiring Medication	90.0% (90/100)	[82.4%, 95.1%]
Hypertension Requiring Medication	71.0% (71/100)	[61.1%, 79.6%]
History of Bleeding Disorder	0.0% (0/100)	[0.0%, 3.6%]
History of GI Bleeding	0.0% (0/100)	[0.0%, 3.6%]
History of TIA	2.0% (2/100)	[0.2%, 7.0%]
History of CVA	6.1% (6/99)	[2.3%, 12.7%]
History of TIA or CVA	8.0% (8/100)	[3.5%, 15.2%]
History of PVD	2.0% (2/100)	[0.2%, 7.0%]
History of Renal Disease	1.0% (1/100)	[0.0%, 5.4%]

Numbers are presented as % (count/sample size), or mean± standard deviation (n)

Abbreviation: CVA=cerebrovascular accident; GI=gastrointestinal; ITT=intent-to-treat; PVD=peripheral vascular disease; TIA=transient ischemic attack

Table X.D3-T2: Cardiac History

Parameter	SYNERGY (N=100)	[95% CI]
Family History of CAD	68.7% (57/83)	[57.6%, 78.4%]
History of PCI	33.0% (33/100)	[23.9%, 43.1%]
History of CABG	1.0% (1/100)	[0.0%, 5.4%]

Table X.D3-T2: Cardiac History

Parameter	SYNERGY (N=100)	[95% CI]
History of Myocardial Infarction	18.0% (18/100)	[11.0%, 26.9%]
History of Congestive Heart Failure	12.0% (12/100)	[6.4%, 20.0%]
NYHA Classification		
I	9.0% (9/100)	[4.2%, 16.4%]
II	2.0% (2/100)	[0.2%, 7.0%]
III	0.0% (0/100)	[0.0%, 3.6%]
IV	0.0% (0/100)	[0.0%, 3.6%]
Unknown	1.0% (1/100)	[0.0%, 5.4%]
History of Arrhythmia	20.0% (20/100)	[12.7%, 29.2%]
History of Atrial Fibrillation	6.0% (6/100)	[2.2%, 12.6%]
Current Anginal Status		
Stable Angina	69.0% (69/100)	[59.0%, 77.9%]
CCS Classification		
1	30.0% (30/100)	[21.2%, 40.0%]
2	33.0% (33/100)	[23.9%, 43.1%]
3	3.0% (3/100)	[0.6%, 8.5%]
4	2.0% (2/100)	[0.2%, 7.0%]
Unknown	1.0% (1/100)	[0.0%, 5.4%]
Unstable Angina	14.0% (14/100)	[7.9%, 22.4%]
Braunwald Classification		
IA	0.0% (0/100)	[0.0%, 3.6%]
IB	4.0% (4/100)	[1.1%, 9.9%]
IC	1.0% (1/100)	[0.0%, 5.4%]
IIA	0.0% (0/100)	[0.0%, 3.6%]
IIB	2.0% (2/100)	[0.2%, 7.0%]
IIC	0.0% (0/100)	[0.0%, 3.6%]
IIIA	0.0% (0/100)	[0.0%, 3.6%]
IIIB	7.0% (7/100)	[2.9%, 13.9%]
IIIC	0.0% (0/100)	[0.0%, 3.6%]
Unknown	0.0% (0/100)	[0.0%, 3.6%]
No Angina	17.0% (17/100)	[10.2%, 25.8%]
Silent Ischemia	8.8% (8/91)	[3.9%, 16.6%]
MI ^a	26.0% (26/100)	[17.7%, 35.7%]
LVEF Measurement (%)	53.29±12.34 (42)	[49.55, 57.02]
History of Multivessel Disease	38.0% (38/100)	[28.5%, 48.3%]
History of Left Main Disease	5.0% (5/100)	[1.6%, 11.3%]

Numbers are presented as % (count/sample size), or mean± standard deviation (n) (minimum, maximum).

a: The indication for the procedure was considered to be an MI if any of the following were met::

- 1) Site indicated in the CRF that the indication for the procedure was an MI, or
- 2) Subjects have positive pre-procedure CK-MB (>1URL), or
- 3) Subjects have positive pre-procedure Troponin (>1URL), or
- 4) Subjects have positive pre-procedure CK (>1URL) and both pre-procedure CK-MB and Troponin were not measured.

Abbreviation: ITT=intent-to-treat; CAD=coronary artery disease; MI=myocardial infarction; CHF=congestive heart failure; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery; URL=upper reference limit; LVEF= Left Ventricular Ejection Fraction

D4. Safety and Effectiveness Results

Principal safety and effectiveness results through 9 months are summarized below and in the **Table X.D4-T1** below. Patient flow is shown in the diagram following the table.

- For the primary endpoint analysis, the ITT rate of in-stent late loss at 9 months post-index procedure was 0.23±0.34 mm (in 95 subjects) which was significantly less than the performance goal of 0.40 mm (P<0.0001)
- The intent-to-treat and per protocol patient populations were identical
- There were no deaths
- Five subjects had peri-procedural non-Q-wave myocardial infarctions (5.0%) based on the protocol definition
- No patient experienced a definite, probable or possible stent thrombosis through 9 months
- The technical success rate was 100.0% (116/116)
- The clinical procedural success rate was 95.0% (95/100)
- There were no instances of longitudinal stent deformation through 9 months

Table X.D4-T1: EVOLVE II QCA Principal Effectiveness and Safety Results, (9 Months)

Events	SYNERGY	[95% CI]
9-Month Clinical Endpoints		
All Death or MI	5.0% (5/100)	[1.6%, 11.3%]
All Death	0.0% (0/100)	[0.0%, 3.6%]
MI ^a	5.0% (5/100)	[1.6%, 11.3%]
Q-wave MI	0.0% (0/100)	[0.0%, 3.6%]
Non-Q-wave MI	5.0% (5/100)	[1.6%, 11.3%]
TVR	3.0% (3/100)	[0.6%, 8.5%]
TLR	1.0% (1/100)	[0.0%, 5.4%]
Non-TLR TVR	2.0% (2/100)	[0.2%, 7.0%]
Cardiac Death or MI	5.0% (5/100)	[1.6%, 11.3%]
TLF	6.0% (6/100)	[2.2%, 12.6%]
TVF	8.0% (8/100)	[3.5%, 15.2%]
Definite, Probable or Possible ARC Stent Thrombosis	0.0% (0/100)	[0.0%, 3.6%]
Stroke (Ischemic)	2.0% (2/100)	[0.2%, 7.0%]
Peri-procedural Endpoints		
Procedural Success	95.0% (95/100)	[88.7%, 98.4%]
Technical Success	100.0% (116/116)	[96.9%, 100.0%]
Longitudinal Stent Deformation	0.0% (0/124)	[0.0%, 2.9%]
In-stent Percent Diameter Stenosis	7.18±8.61 (116)	[5.62, 8.75]
In-segment Percent Diameter Stenosis	20.38±7.78 (116)	[18.97, 21.80]
In-stent Minimum Lumen Diameter	2.49±0.43 (116)	[2.42, 2.57]
In-segment Minimum Lumen Diameter	2.15±0.44 (116)	[2.07, 2.23]
In-stent Acute Gain	1.63±0.41 (116)	[1.56, 1.71]
In-segment Acute Gain	1.29±0.42 (116)	[1.21, 1.37]
9-Month Angiographic Endpoints		
In-stent Percent Diameter Stenosis	13.54±12.49 (110)	[11.21, 15.88]
In-segment Percent Diameter Stenosis	22.39±11.27 (110)	[20.29, 24.50]

Events	SYNERGY	[95% CI]
In-stent Binary Restenosis	1.8% (2/110)	[0.2%, 6.4%]
In-segment Binary Restenosis	3.6% (4/110)	[1.0%, 9.0%]
In-stent Minimum Lumen Diameter	2.29±0.46 (110)	[2.20, 2.37]
In-segment Minimum Lumen Diameter	2.06±0.46 (110)	[1.98, 2.15]
In-stent late loss	0.22±0.33 (110)	[0.16, 0.28]
In-segment late loss	0.10±0.30 (110)	[0.05, 0.16]
Stent Fracture	0.0% (0/124)	[0.0%, 2.9%]
Longitudinal Stent Deformation	0.0% (0/124)	[0.0%, 2.9%]
9-Month IVUS Endpoints		
Incomplete Apposition	6.5% (6/92)	[2.4%, 13.7%]
Percent Net Volume Obstruction	5.19±5.67 (93)	[4.04, 6.34]
Stent Volume	177.76±86.33 (93)	[160.22, 195.31]
Vessel Volume	328.90±159.79 (92)	[296.24, 361.55]
Lumen Volume	168.10±81.28 (93)	[151.59, 184.62]

Note: Intent-to-Treat and Per-Protocol subjects are identical.

All TVR and TLR were treated by PCI. Clinical endpoints and procedure success are subject-based.

Technical success is lesion-based. Stent fracture and longitudinal stent deformation are stent-based (analyzed by QCA). Angiographic endpoints are lesion-based. IVUS endpoints are segment-based.

a: Spontaneous MI: rise and/or fall of cardiac biomarkers with ≥ 1 value >99 th percentile of the URL + evidence of myocardial ischemia. Peri-PCI MI: ≥ 1 of the following: i) CK-MB $>3X$ URL within 48 hours, ii) new pathological Q waves, iii) autopsy evidence.

E. NG PROMUS Clinical Overview

E1. Study Design

NG PROMUS was a prospective, single arm, multicenter, observational study designed to evaluate clinical and peri-procedural angiographic and IVUS outcomes for the Promus PREMIER Everolimus-Eluting Platinum Chromium Coronary Stent System in the treatment of subjects with atherosclerotic lesions ≤ 34 mm in length (by visual estimate) in native coronary arteries ≥ 2.50 mm to ≤ 4.00 mm in diameter (by visual estimate).

Clinical Inclusion and Exclusion Criteria

Table X.E1-T1: Inclusion and Exclusion Criteria, NG PROMUS

Clinical Inclusion Criteria	CI1. Subject must be at least 18 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed CI3. Subject is eligible for percutaneous coronary intervention (PCI) CI4. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia CI5. Subject is an acceptable candidate for coronary artery bypass grafting (CABG) CI6. Subject is willing to comply with all protocol-required follow-up evaluation
Angiographic Inclusion Criteria	AI1. Target lesion(s) must be located in a native coronary artery with a visually estimated reference vessel diameter (RVD) ≥ 2.50 mm and ≤ 4.0 mm AI2. Target lesion(s) length must be ≤ 34 mm (by visual estimate) AI3. Target lesion(s) must have visually estimated stenosis $\geq 50\%$ and $< 100\%$ with thrombolysis in Myocardial Infarction (TIMI) flow > 1 and one of the following

Table X.E1-T1: Inclusion and Exclusion Criteria, NG PROMUS

	<p>(stenosis $\geq 70\%$, abnormal fractional flow reserve (FFR), abnormal stress test or imaging stress test, or elevated biomarkers) prior to procedure</p> <p>A14. Coronary anatomy is likely to allow delivery of a study device to the target lesions(s)</p> <p>A15. The first lesion treated must be successfully pre-dilated/pretreated</p> <p>Note: Successful pre-dilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C.</p>
<p>Clinical Exclusion Criteria</p>	<p>CE1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI)</p> <p>CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina</p> <p>CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant</p> <p>CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure</p> <p>CE5. Planned PCI (including staged procedures) or CABG after the index procedure</p> <p>CE6. Subject previously treated at any time with intravascular brachytherapy</p> <p>CE7. Subject has a known allergy to contrast (that cannot be adequately pre-medicated) and/or the trial stent system or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel, everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors, or aspirin)</p> <p>CE8. Subject has one of the following (as assessed prior to the index procedure):</p> <ul style="list-style-type: none"> • Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 24 months • Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) • Planned procedure that may cause non-compliance with the protocol or confound data interpretation <p>CE9. Subject is receiving chronic (≥ 72 hours) anticoagulation therapy (i.e., heparin, coumadin) for indications other than acute coronary syndrome</p> <p>CE10. Subject has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³</p> <p>CE11. Subject has a white blood cell (WBC) count $< 3,000$ cells/mm³</p> <p>CE12. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis</p> <p>CE13. Subject is on dialysis or has baseline serum creatinine level > 2.0 mg/dL (177μmol/L)</p> <p>CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions</p> <p>CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months</p> <p>CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding</p> <p>CE17. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) at the time of the index procedure</p> <p>CE18. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint</p> <p>CE19. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure</p> <p>CE20. Subject 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)</p> <p>CE21. Subject 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)</p>

Table X.E1-T1: Inclusion and Exclusion Criteria, NG PROMUS

Angiographic Exclusion Criteria (visual estimate)	<p>AE1. Planned treatment of more than 3 lesions.</p> <p>AE2. Planned treatment of lesions in more than 2 major epicardial vessels</p> <p>AE3. Planned treatment of a single lesion with more than 1 stent</p> <p>AE4. Subject has 2 target lesions in the same vessel that are separated by less than 15 mm (by visual estimate)</p> <p>AE5. Target lesion(s) is located in the left main</p> <p>AE6. Target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate.</p> <p>AE7. Target lesion(s) is located within a saphenous vein graft or an arterial graft</p> <p>AE8. Target lesion(s) will be accessed via a saphenous vein graft or arterial graft</p> <p>AE9. Target lesion(s) with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing</p> <p>AE10. Target lesion(s) treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent)</p> <p>AE11. Target lesion(s) is restenotic from a previous stent implantation or study stent would overlap with a previous stent</p> <p>AE12. Subject has unprotected left main coronary artery disease (>50% diameter stenosis)</p> <p>AE13. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon atherectomy) within 24 hours prior to the index procedure</p> <p>AE14. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)</p>
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Follow-up Schedule

Clinical follow-up by telephone at 30 days

Clinical Endpoints

Adverse events are collected throughout the study with a pre-specified subset of events adjudicated by an independent Clinical Events Committee.

The Primary Endpoint is technical success rate, defined as successful delivery and deployment of the study stent to the target lesion, without balloon rupture or stent embolization, and post-procedure diameter stenosis of <30% assessed in 2 near-orthogonal projections with TIMI 3 flow in the target lesion, as visually assessed by the physician.

E2. Accountability of NG PROMUS Cohort

Table X.E2-T1 shows subject disposition. There were 100 subjects enrolled (intent-to-treat [ITT] analysis set) and implanted (as-treated analysis set) at 9 investigative centers in Australia, New Zealand, and Singapore from 20-Nov-2012 to 12-Mar-2013.

Clinical follow-up at 30 days was 99.0% (98/99). One subject died before the 30-day follow-up window and 1 subject missed the 30-day visit.

Table X.E2-T1: Subject Disposition, Clinical Follow-up Compliance Intent-to-Treat, (N=100)

	Subjects
Subjects enrolled (Intent-to-Treat analysis set)	100

	Subjects
Subjects treated with at least 1 study stent	100
Death ≤30 days with no 30-day clinical follow-up performed	1
Eligible for 30-day clinical follow-up ^a	99
30-Day clinical follow-up visit completed ^b	99.0% (98/99)
Office Visit	11
Telephone contact	87
No 30-Day clinical follow-up performed	1
Premature discontinuation	0
Withdrew consent	0
Lost to follow-up	0
Adverse event	0
Investigator discretion	0
Other	0
Death >30 days	0
Missed 30-day follow-up visit	1
30-Day clinical follow-up or death ^c	99.0% (99/100)

Numbers are n or % (count/sample size).

a: Patients who died prior to completion of follow-up window and prior to completing a 30-day 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 30-day clinical follow-up (excludes deaths before 30 days)

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

Abbreviation: ITT=intent-to-treat

E3. Study Population Demographics and Baseline Parameters

Table X.E3-T1 presents demographics and baseline clinical characteristics for the ITT analysis set (N=100). The ITT population was predominantly male (85.0%) with a history of medically treated hyperlipidemia (78.0%) and hypertension (70.0%). Medically treated diabetic subjects accounted for 16.0% of ITT subjects. Unstable angina was reported for 25.0% of subjects and 16.0% had a history of MI.

Table X.E3-T1: Baseline Demographics and General Medical History, ITT Analysis Set

Parameter	NG PROMUS
Male	85.0% (85/100)
Age (years)	61.72±9.73 (100) (38, 81)
Weight (kg)	87.94±19.85 (100) (50, 179)
Ethnicity and Race	
Hispanic or Latino	2.0% (2/100)
Caucasian	72.0% (72/100)
Asian	13.0% (13/100)
Black, of African Heritage	1.0% (1/100)
Native Hawaiian or Other Pacific Islander	5.0% (5/100)
American Indian or Alaska Native	0.0% (0/100)
Other	6.0% (6/100)
Not disclosed	1.0% (1/100)
Medical History	
Smoking Status	
Current	14.0% (14/100)
Previous	42.0% (42/100)

Parameter	NG PROMUS
Never	44.0% (44/100)
Unknown	0.0% (0/100)
Current diabetes mellitus	18.0% (18/100)
Diabetes treated with diet only	6.0% (6/100)
Diabetes (medically treated)	16.0% (16/100)
Insulin	2.0% (2/100)
Oral medications (no insulin)	16.0% (16/100)
Injectable agent (other than insulin)	0.0% (0/100)
Diabetes with treatment unknown	0.0% (0/100)
History of hyperlipidemia (medically treated)	78.0% (78/100)
History of hypertension (medically treated)	70.0% (70/100)
History of bleeding disorder	0.0% (0/100)
Gastrointestinal	0.0% (0/100)
Hematologic dyscrasia	0.0% (0/100)
Cardiac History	
Family history of coronary artery disease	51.0% (51/100)
History of myocardial infarction	16.0% (16/100)
History of congestive heart failure	2.0% (2/100)
Current Angina Status	
Angina, stable	51.0% (51/100)
Angina, unstable	25.0% (25/100)
Angina, none	21.0% (21/100)
Angina, unknown	3.0% (3/100)
Silent ischemia	6.0% (6/100)
Previous percutaneous coronary intervention	23.0% (23/100)
Previous coronary artery bypass graft	5.0% (5/100)
History of arrhythmia	6.0% (6/100)
Left ventricular ejection fraction (%)	63.57±11.22 (49) (40.00, 90.00)
History of multivessel disease	32.0% (32/100)
Neurologic History	
Transient ischemic attack	1.0% (1/100)
Cerebrovascular accident	2.0% (2/100)
Renal and Peripheral History	
History of renal disease	1.0% (1/100)
History of peripheral vascular disease	3.0% (3/100)

Numbers are presented as mean±standard deviation (n) or % (count/sample size).

Abbreviation: ITT=intent-to-treat

E4. Safety and Effectiveness Results

Principal safety and effectiveness results through 30days are summarized below and in the table following.

- Technical success was 99.2% (118/119 lesions)
- Clinical procedural success was 99.0% (99/100)
- There was a single death, which was adjudicated by the CEC as a cardiac death.
- Through 30 days, the protocol MI rate was 9.0% (9/100) and the PLATINUM MI rate was 1.0% (1/100); all of the MIs occurred in hospital and all were non-Q-wave MIs.
- There were no revascularizations and no stent thromboses

Table X.E4-T1: NG PROMUS 30-Day Clinical Results

Parameter	NG PROMUS (N=100)	
Primary endpoint (technical success)	99.2% (118/119 lesions)	
Clinical endpoints	In-Hospital	30 Days
All death, MI, TVR	1.0% (1/100)	2.0% (2/100)
All death or MI	1.0% (1/100)	2.0% (2/100)
All death	0.0% (0/100)	1.0% (1/100)
Cardiac death	0.0% (0/100)	1.0% (1/100)
Non-cardiac death	0.0% (0/100)	0.0% (0/100)
MI	1.0% (1/100)	1.0% (1/100)
Q-wave MI	0.0% (0/100)	0.0% (0/100)
Non-Q-wave MI	1.0% (1/100)	1.0% (1/100)
TVR, overall	0.0% (0/100)	0.0% (0/100)
TLR, overall	0.0% (0/100)	0.0% (0/100)
Non-TLR TVR, overall	0.0% (0/100)	0.0% (0/100)
Cardiac death, MI	1.0% (1/100)	2.0% (2/100)
TLF	1.0% (1/100)	2.0% (2/100)
TVF	1.0% (1/100)	2.0% (2/100)
ARC ST (definite/probable)	0.0% (0/100)	0.0% (0/100)
Peri-procedural endpoints	NG PROMUS (N=100)	
Clinical procedural success	99.0% (99/100)	
Quantitative coronary angiography (N=119 Lesions; N=127 Stents)		
Pre-procedure		
Lesion length (mm)	16.05±7.14 (119)	
Reference vessel diameter (mm)	2.78±0.45 (119)	
MLD, in-lesion (mm)	0.85±0.29 (119)	
Diameter stenosis (%)	69.12±9.69 (119)	
Post-procedure		
MLD, in-stent (mm)	2.69±0.43 (119)	
MLD, in-segment (mm)	2.31±0.46 (119)	
Acute gain, in-stent (mm)	1.84±0.45 (119)	
Acute gain, in-segment (mm)	1.46±0.47 (119)	
Diameter stenosis, in-stent (%)	3.86±8.43 (119)	
Diameter stenosis, in-segment (%)	18.14±7.90 (119)	
Intravascular ultrasound		
Incomplete stent apposition	12.9% (13/101)	
Vessel area (mm ²)	15.10±4.34 (99) (7.57, 28.35)	
Stent area (mm ²)	7.83±2.38 (101) (3.72, 15.89)	
Lumen area (mm ²)	7.76±2.25 (100) (3.72, 13.51)	
Vessel volume (mm ³)	354.34±181.60 (99) (98.40, 975.05)	
Stent volume (mm ³)	185.30±91.75 (101) (49.23, 460.78)	
Lumen volume (mm ³)	182.62±87.93 (100) (49.23, 459.36)	
In-stent net volume obstruction (%)	0.00±0.01 (100) (0.00, 0.12)	

Numbers are presented as % (count/sample size) or mean±standard deviation (n).
MLD=minimum lumen diameter.

F. Prevalence of CAD and Outcome Differences by Gender and Race

As noted in the FDA Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies, issued August 22, 2014, certain medical products elicit different responses in women compared to men. Differences may be attributable to intrinsic factors (e.g., genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g., diet, sociocultural issues, environment) or interactions between these factors. In order to understand any potential sex or gender differences which may be relevant to the clinical evaluation of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System, Boston Scientific provides background information on the following for the condition which the device is intended to treat:

- Sex/gender-specific prevalence;
- Sex/gender-specific diagnosis and treatment patterns;
- Identification of proportions of women target indication;
- Identification of any known clinically significant sex or gender differences in
- Outcomes related to either safety or effectiveness.

A summary of this information has been included in the draft labeling.

F1. Sex/gender-specific prevalence:

An estimated 15.4 million Americans ≥ 20 years of age have coronary artery disease (CAD). Total CAD prevalence is 6.4% in US adults ≥ 20 years of age. CAD prevalence is 7.9% for men and 5.1%¹.

F2. Sex/gender-specific (and, if known, race-specific) diagnosis and treatment patterns:

Gender-specific differences have been reported in the symptom profile, diagnosis, and treatment of CAD. Compared with men, the clinical outcomes in women who present with cardiac symptoms are less favorable. This disparity has been attributable to both biological and social factors.

The incidence of CAD in women is lower than in men, but rises steadily after the fifth decade and nearly equalizes between the genders by the seventh decade of life. Further, the distribution of CAD risk factors varies between men and women across age ranges. Failure to consider these differences may have contributed to the belief that women are at lower risk of CAD compared with men. In addition, gender differences exist in clinical presentation of cardiovascular symptoms, with 'atypical' presentations being more common in women. As a result, there may be a delay in seeking medical care for women. Even when they do seek care, the symptoms may not be recognized as having a cardiac cause, resulting in less aggressive treatment approaches.

The diagnosis of CAD in women is challenged by a higher false-positive rate of exercise tolerance testing (ETT). Furthermore, the higher incidence of non-occlusive CAD in women results in an absence of angiographic findings in

symptomatic women leading to a search for non-cardiac etiology. Once diagnosed, poorer revascularization outcomes have been reported in women potentially due to smaller coronary arteries and increased baseline comorbidities (including advanced age, diabetes, hypertension, and peripheral vascular disease) compared with men.

Identification of proportions of women target indication:

Women and minority subjects have been under-represented in past prospective clinical trials evaluating coronary revascularization strategies. Boston Scientific conducted a retrospective pooled analysis of subjects enrolled in 5 randomized trials and 2 ‘real world’ registries to evaluate the influence of gender on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent.² Of the 2,271 subjects pooled from the randomized trials, 665 (29.3%) were women. The proportion of women included in our studies is reflective of the 15-35% enrollment of women reported in other PCI trials.

F3. Identification of any known clinically significant sex or gender differences in outcomes related to either safety or effectiveness:

Early studies of subjects undergoing coronary artery bypass graft and coronary angioplasty reported higher in-hospital mortality and increased risk for adverse outcomes in women compared to men.^{3,4} With the advent of stents and improved procedural pharmacotherapy, overall mortality and the extent of the gender differences decreased.⁵ Randomized trials of DES demonstrated a further narrowing of the gender gap as revascularization with DES significantly reduced the incidence of in-stent restenosis and the need for repeat revascularization compared with bare metal stents equally in men and women.^{6,7} To determine the influence of sex on long-term DES outcomes we compared gender-based outcomes in subjects receiving paclitaxel-eluting stents in randomized trials through 5 years.² This study demonstrated that compared with men, women had more adverse baseline characteristics but similar safety and effectiveness outcomes through 5 years (Figure 6.8-F1).

Additionally, an analysis of subjects treated with everolimus-eluting stents in the EVOLVE II RCT study was performed to assess the impact of gender on outcomes. Difference in treatment and gender are observed. Despite these differences, the overall conclusions of the trial regarding both safety and effectiveness of the SYNERGY Stent can be generalized to males and females. However, the influence of gender on long-term drug-eluting stent outcomes has not been fully elucidated.

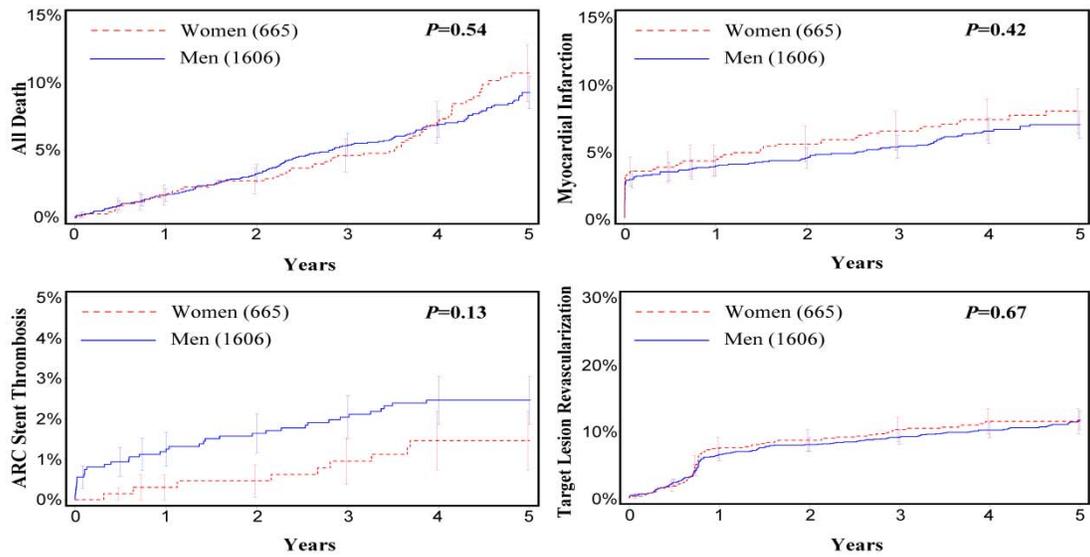


Figure X.F3-F1: Kaplan-Meier estimates of 5-year cumulative rates of clinical outcomes for women versus men for subjects receiving paclitaxel-eluting stents in the randomized trials

In order to evaluate the influence of sex or gender on principal effectiveness and safety endpoints through the 12-month primary endpoint for EVOLVE II RCT, Boston Scientific has performed sex/gender-specific subgroup analyses.

In the EVOLVE II RCT Trial there were 478 female and 1206 male subjects. Table X.F4-T1 shows clinical outcomes through 12-months in female and male subjects. The pattern of results seen in the overall analysis set was maintained and there were no statistically significant differences between the PROMUS Element Plus and SYNERGY groups at 12 months. The gender subgroup analyses are intended as exploratory analyses only.

Table X.F3-T1: Principal Effectiveness and Safety Endpoints through 12 Months, EVOLVE II RCT Male and Female Subjects, Intent-to-Treat (N=1684)

12-Month Clinical Endpoints	Male Subjects		Female Subjects	
	SYNERGY (N=597 Subjects)	PROMUS Element Plus (N=609 Subjects)	SYNERGY (N=249 Subjects)	PROMUS Element Plus (N=229 Subjects)
All Death, MI, TVR	9.7% (57/586)	7.8% (46/589)	8.1% (20/246)	10.0% (22/219)
All Death or MI	6.5% (38/586)	4.9% (29/589)	5.7% (14/246)	8.2% (18/219)
All Death	1.0% (6/586)	0.8% (5/589)	1.2% (3/246)	1.8% (4/219)
Cardiac Death	0.3% (2/586)	0.5% (3/589)	0.8% (2/246)	1.8% (4/219)
Non-Cardiac Death	0.7% (4/586)	0.3% (2/589)	0.4% (1/246)	0.0% (0/219)
MI	5.8% (34/586)	4.1% (24/589)	4.5% (11/246)	7.3% (16/219)
Related to TV	4.8% (28/586)	4.1% (24/589)	3.3% (8/246)	6.4% (14/219)
Unknown relationship	0.2% (1/586)	0.2% (1/589)	0.0% (0/246)	0.0% (0/219)
Not related to TV	1.0% (6/586)	0.0% (0/589)	1.2% (3/246)	0.9% (2/219)
Q-wave MI	0.3% (2/586)	0.0% (0/589)	0.0% (0/246)	0.9% (2/219)
Related to TV	0.3% (2/586)	0.0% (0/589)	0.0% (0/246)	0.9% (2/219)
Not related to TV	0.0% (0/586)	0.0% (0/589)	0.0% (0/246)	0.0% (0/219)
Non-Q-wave MI	5.5% (32/586)	4.1% (24/589)	4.5% (11/246)	6.4% (14/219)
Related to TV	4.4% (26/586)	4.1% (24/589)	3.3% (8/246)	5.5% (12/219)
Unknown relationship	0.2% (1/586)	0.2% (1/589)	0.0% (0/246)	0.0% (0/219)
Not related to TV	1.0% (6/586)	0.0% (0/589)	1.2% (3/246)	0.9% (2/219)
TVR, Overall	4.1% (24/586)	3.9% (23/589)	3.3% (8/246)	2.7% (6/219)
TLR, Overall	2.7% (16/586)	1.7% (10/589)	2.4% (6/246)	1.8% (4/219)
Non-TLR TVR, Overall	1.9% (11/586)	2.5% (15/589)	1.6% (4/246)	1.4% (3/219)
Cardiac Death or MI	5.8% (34/586)	4.6% (27/589)	5.3% (13/246)	8.2% (18/219)
TLF	7.0% (41/586)	5.6% (33/589)	5.7% (14/246)	8.7% (19/219)
TVF	8.7% (51/586)	7.8% (46/589)	6.9% (17/246)	9.1% (20/219)
ARC Stent Thrombosis	0.3% (2/586)	0.7% (4/589)	1.2% (3/246)	0.9% (2/219)

Definite or Probable	0.2% (1/586)	0.7% (4/589)	0.8% (2/246)	0.5% (1/219)
Definite	0.2% (1/586)	0.2% (1/589)	0.4% (1/246)	0.5% (1/219)
Probable	0.0% (0/586)	0.5% (3/589)	0.4% (1/246)	0.0% (0/219)
Possible	0.2% (1/586)	0.0% (0/589)	0.4% (1/246)	0.5% (1/219)
Stroke	0.9% (5/586)	0.7% (4/589)	0.4% (1/246)	1.4% (3/219)
Ischemic Stroke	0.9% (5/586)	0.7% (4/589)	0.0% (0/246)	1.4% (3/219)
Hemorrhagic Stroke	0.0% (0/586)	0.0% (0/589)	0.0% (0/246)	0.0% (0/219)
Undetermined Stroke	0.0% (0/586)	0.0% (0/589)	0.4% (1/246)	0.0% (0/219)
Longitudinal Stent Deformation	0.1% (1/787)	0.1% (1/793)	0.0% (0/324)	0.0% (0/286)

Additionally, since the EVOLVE II RCT involves a prospective control group, Boston Scientific has performed statistical testing to evaluate potential interaction between treatment and sex/gender. Table X.F4-T2 shows that the treatment effect is consistent across genders.

Table X.F3-T2: Summary of 12-Month TLF for EVOLVE II RCT Female and Male Subgroups, All Subjects, Intent-to-Treat (N=1684)

TLF at 12 Months	PROMUS Element Plus (N=838)	SYNERGY (N=846)	Relative Risk [95% CI]	Difference [95% CI]	P-value	Interaction P-value
	(N=229)	(N=249)				0.1156
Female (N=478)	8.7% (19/218)	5.7% (14/244)	0.66 [0.34, 1.28]	-3.0% [-7.7%, 1.8%]	0.2147	
	(N=609)	(N=597)				
Male (N=1206)	5.6% (33/586)	7.0% (41/582)	1.25 [0.80, 1.95]	1.4% [-1.4%, 4.2%]	0.3215	

“p-Value” tests the difference between treatments for each subgroup from the chi-square test.

“Interaction p-Value” tests the treatment by subgroup interaction from the chi-square test from logistic regression.

G. Financial Disclosure

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 125 Principal Investigators of which none were full-time or part-time employees of the sponsor and 13 (including 5 sub-investigators) 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: 10
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 3

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.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Device Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The safety and effectiveness of the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (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. These tests revealed the following information:

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 vivo* 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 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. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System of improving the patient symptoms outweigh the probable risks associated with use of the device.

Additional factors that were considered in determining the probable risks and benefits of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System included:

- Key clinical data supporting the safety and effectiveness of the SYNERGY stent were obtained from the EVOLVE II randomized controlled trial, where the primary endpoint of 12-month TLF (target lesion failure) in the SYNERGY stent was compared to the 12-month TLF rate in the control device (PROMUS Element Plus):
 - The intent-to-treat TLF rate was observed in 6.5% of PROMUS Element Plus and 6.7% SYNERGY treated subjects (difference=0.2%; 97.5% upper confidence bound=2.68%; P=0.0005 for non-inferiority), and
 - The per protocol rate was observed in 6.4% of PROMUS Element Plus and 6.4% SYNERGY treated subjects (difference=0.0%; 97.5% upper confidence bound=2.51%; P=0.0003 for non-inferiority).

These data demonstrate that the SYNERGY stent is non-inferior to the PROMUS Element Plus Stent, and is of clinical benefit to patients undergoing PCI procedures.

- The rates of individual important safety events including death, MI, and stent thrombosis were low and comparable to the control group.

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 SYNERGY stent were found to be similar to the risks and benefits of these devices.

In conclusion, given the available information above, the data support that the probable benefits of the SYNERGY stent, when used as indicated, outweigh the probable risks.

C. 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. Data from the EVOLVE Clinical Program support the safety and effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions when used in accordance with the Directions for Use (DFU).

XIII. CDRH DECISION

CDRH issued an approval order on October 2, 2015. The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

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

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