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SYNERGY™

MONORAIL™

OVER-THE-WIRE™

Everolimus-Eluting Platinum Chromium Coronary Stent System

℞ ONLY

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

This device is supplied in sterile condition. All materials inside the sterile barrier pouch (the delivery system and stent, as well as the carrier tube and pouch liner) are sterile. The external surface of the sterile barrier pouch, as well as the product carton, should not be considered sterile.

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1 WARNING:

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

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2 DEVICE DESCRIPTION:

The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System) is a device/drug combination product consisting of a drug/polymer-coated balloon expandable stent, pre-mounted on a Monorail (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr), which consists of platinum, chromium, iron, nickel, and molybdenum. The characteristics of the SYNERGY Stent System are described in Table 2.1. SYNERGY Stent System Product Description:

Table 2.1 SYNERGY™ Stent System Product Description

	SYNERGY Monorail™ Stent Delivery System	SYNERGY Over-the-Wire Stent Delivery System
Drug Coated Stent		
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, 4.50* and 5.00*	2.25, 2.50, 2.75, 3.00, 3.50, 4.00
Stent Material	Platinum Chromium Alloy (PtCr) (PtCr alloy components: platinum, chromium, iron, nickel, and molybdenum)	
Stent Strut Thickness	2.25 mm - 2.75 mm: 0.0029 inches (0.074 mm) 3.00 mm - 3.50 mm: 0.0031 inches (0.079 mm) 4.00 mm - 5.00 mm: 0.0032 inches (0.081 mm)	2.25 mm - 2.75 mm: 0.0029 inches (0.074 mm) 3.00 mm - 3.50 mm: 0.0031 inches (0.079 mm) 4.00 mm: 0.0032 inches (0.081 mm)
Drug Product	An abluminal (outer surface of the stent in contact with the vessel wall) 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 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 for all Diameters: 11 atm (1117 kPa)	
	Rated Burst Inflation Pressure: •Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) •Diameters 3.00 mm – 5.00 mm: 16 atm (1620 kPa)	Rated Burst Inflation Pressure: •Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) •Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)
Catheter Shaft Outer Diameter	Proximal: 2.1F (0.70 mm) Distal: 2.25 – 2.75 mm: 2.6F (0.90 mm) 3.00 mm: •8 – 28 mm: 2.6F (0.90 mm) •32 – 38 mm: 2.7F (0.95 mm) 3.50 mm: •8 – 20 mm: 2.6F (0.90 mm) •24 – 38 mm: 2.7F (0.95 mm) 4.00 mm - 5.00 mm: 2.7F (0.95 mm)	3.2F (1.07 mm) proximal for 2.25 to 3.50 mm sizes 3.4F (1.15 mm) proximal for 4.00 mm sizes 2.4F (0.82 mm) distal for 2.25 to 2.75 mm sizes 2.7F (0.92 mm) distal for 3.00 to 4.00 mm sizes
Guide Catheter Compatibility (ID)	2.25 - 4.00 mm: ≥5F (0.056 inches/1.42 mm) 4.50 - 5.00 mm: ≥6F (0.066 inches/1.68 mm)	≥6F (0.066 inches/1.68 mm)

* The 4.50 mm and 5.00 mm diameter is not available in 8 mm and 38 mm lengths.

2.1 User Information

Only Physicians who have received adequate training should perform implantation of the stent.

2.2 Non-Pyrogenic

The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System is sterile, non-pyrogenic in unopened, undamaged packaging.

2.3 Device Component Description

The SYNERGY Stent System consists of a platinum chromium stent platform with an abluminal drug/polymer coating mounted onto Monorail and Over-the-Wire Delivery System.

The SYNERGY Stent System is available in three stent models, each engineered for specific diameters to provide consistent stent-to-artery ratios across the range of reference vessel diameters indicated:

- Small Vessel (SV): 2.25 mm, 2.50 mm and 2.75 mm
- Workhorse (WH): 3.00 mm, 3.50 mm
- Large Vessel (LV): 4.00 mm, 4.50 mm and 5.00 mm

Contents for (1) SYNERGY Monorail Stent System

• One (1) SYNERGY Monorail Stent System

• One (1) Flushing needle with luer fitting

Contents for (1) SYNERGY Over-the-Wire Stent System

• One (1) SYNERGY Over-the-Wire Stent System

2.4 Drug Component Description

The stent component of the SYNERGY Stent System is a PtCr stent with a drug/polymer coating. The coating is comprised of a bioabsorbable polymer matrix that contains an active pharmaceutical ingredient (everolimus). This is the same active pharmaceutical ingredient as is used in PROMUS™ (XIENCE V™), PROMUS Element™, PROMUS Element™ Plus and Promus PREMIER™ stent systems.
See section 2.3.1 **Everolimus** and 2.3.2 **Polymer Carrier** sections for descriptions of drug and polymer, respectively.

2.4.1 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 2.1.

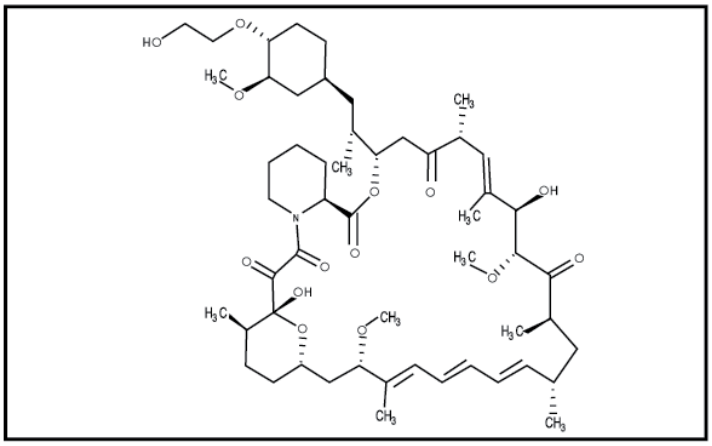

Figure 2.1 The Chemical Structure of Everolimus

2.4.2 Polymer Carrier

The SYNERGY Stent is coated on the abluminal stent surface (surface in contact with vessel wall) with a bioabsorbable drug matrix. The bioabsorbable drug matrix is composed of PLGA [poly (DL-lactide-co-glycolide)] mixed with everolimus. The chemical structure of PLGA is shown below in Figure 2.2. In vivo studies support that the polymer degradation is essentially complete by 4 months.

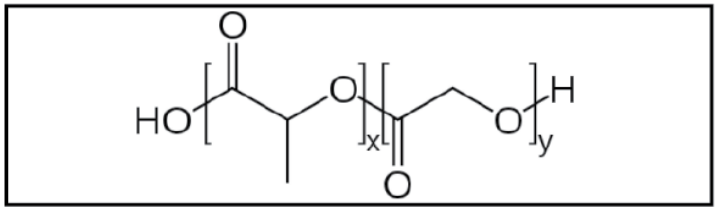

Figure 2.2 The Chemical Structure of PLGA

2.4.3 Product Matrix and Everolimus Content

Table 2.2 SYNERGY™ Stent System Product Matrix and Everolimus Content

Product Code MR	Product Code OTW	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
H7493926008220	H7493926108220	2.25	8	38.9
H7493926008250	H7493926108250	2.50	8	38.9
H7493926008270	H7493926108270	2.75	8	38.9
H7493926008300	H7493926108300	3.00	8	46.5
H7493926008350	H7493926108350	3.50	8	46.5
H7493926008400	H7493926108400	4.00	8	67.5
H7493926012220	H7493926112220	2.25	12	58.3
H7493926012250	H7493926112250	2.50	12	58.3
H7493926012270	H7493926112270	2.75	12	58.3
H7493926012300	H7493926112300	3.00	12	66.3
H7493926012350	H7493926112350	3.50	12	66.3
H7493926012400	H7493926112400	4.00	12	96.2
H7493926012450		4.50	12	96.2
H7493926012500		5.00	12	96.2
H7493926016220	H7493926116220	2.25	16	77.6
H7493926016250	H7493926116250	2.50	16	77.6
H7493926016270	H7493926116270	2.75	16	77.6
H7493926016300	H7493926116300	3.00	16	92.7
H7493926016350	H7493926116350	3.50	16	92.7
H7493926016400	H7493926116400	4.00	16	124.8
H7493926016450		4.50	16	124.8
H7493926016500		5.00	16	124.8
H7493926020220	H7493926120220	2.25	20	96.9
H7493926020250	H7493926120250	2.50	20	96.9
H7493926020270	H7493926120270	2.75	20	96.9
H7493926020300	H7493926120300	3.00	20	112.5
H7493926020350	H7493926120350	3.50	20	112.5
H7493926020400	H7493926120400	4.00	20	153.5
H7493926020450		4.50	20	153.5
H7493926020500		5.00	20	153.5
H7493926024220	H7493926124220	2.25	24	121.1
H7493926024250	H7493926124250	2.50	24	121.1
H7493926024270	H7493926124270	2.75	24	121.1
H7493926024300	H7493926124300	3.00	24	132.3
H7493926024350	H7493926124350	3.50	24	132.3
H7493926024400	H7493926124400	4.00	24	182.2
H7493926024450		4.50	24	182.2
H7493926024500		5.00	24	182.2
H7493926028220	H7493926128220	2.25	28	140.5
H7493926028250	H7493926128250	2.50	28	140.5
H7493926028270	H7493926128270	2.75	28	140.5
H7493926028300	H7493926128300	3.00	28	158.7
H7493926028350	H7493926128350	3.50	28	158.7
H7493926028400	H7493926128400	4.00	28	210.8
H7493926028450		4.50	28	210.8
H7493926028500		5.00	28	210.8
H7493926032220	H7493926132220	2.25	32	159.8
H7493926032250	H7493926132250	2.50	32	159.8
H7493926032270	H7493926132270	2.75	32	159.8

H749**3926032300**	H749**3926132300**	3.00	32	178.5
H749**3926032350**	H749**3926132350**	3.50	32	178.5
H749**3926032400**	H749**3926132400**	4.00	32	239.5
H749**3926032450**		4.50	32	239.5
H749**3926032500**		5.00	32	239.5
H749**3926038220**	H749**3926138220**	2.25	38	188.9
H749**3926038250**	H749**3926138250**	2.50	38	188.9
H749**3926038270**	H749**3926138270**	2.75	38	188.9
H749**3926038300**	H749**3926138300**	3.00	38	211.6
H749**3926038350**	H749**3926138350**	3.50	38	211.6
H749**3926038400**	H749**3926138400**	4.00	38	287.2

3 INTENDED USE/INDICATIONS FOR USE:

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients, including those at high risk for bleeding, with diabetes mellitus, 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 ≤5.00 mm in diameter in lesions ≤34 mm in length.

4 CONTRAINDICATIONS:

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

- 316L stainless steel, platinum, chromium, iron, nickel or molybdenum
- Everolimus or structurally-related compounds
- The polymer or their individual components (see section 2.4.2 Polymer Carrier)

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 (see Section 6.2, Pre- and Post- Procedure Antiplatelet Regimen for more information).

5 WARNINGS:

- To maintain sterility, the inner package should not be opened or damaged prior to use.
- The use of this product carries the risks associated with coronary artery stenting, including stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

6 PRECAUTIONS:

6.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery is readily available.
- Subsequent stent blockage may require repeat dilation of the arterial segment containing the stent. The long-term outcome following repeat dilation of endothelialized stents is not well characterized.
- Careful consideration should be given to the risks and benefits of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system, visually confirm complete balloon deflation under fluoroscopy. Failure to do so may cause increased stent delivery system withdrawal forces and result in guide catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a rare event and is frequently associated with myocardial infarction (MI) or death. In the clinical trials analysed to date, differences in the incidence of stent thrombosis have not been associated with an increased risk of cardiac death, MI, or all-cause mortality.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed during the EVOLVE clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization,

MI or death. When treating such patients, physicians should be aware of this increased risk and consider available data and the limitations of such data.

• Orally-administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglyceride levels.

6.2 Pre- and Post-Procedure Antiplatelet Regimen

In the EVOLVE II Trial, a $P2Y_{12}$ inhibitor was administered pre-procedure and for a period of 6 months post procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with the $P2Y_{12}$ inhibitor and was required to be continued indefinitely to reduce the risk of thrombosis.

The optimal duration of antiplatelet therapy, specifically $P2Y_{12}$ inhibitor therapy, is unknown and DES thrombosis may still occur despite continuation of therapy beyond current professional society guidelines. Data from several studies suggest that a longer duration of antiplatelet therapy than was recommended post-procedurally in DES pivotal clinical trials may be beneficial. Provided herein are recommendations for post-procedural antiplatelet therapy from the 2016 ACC/AHA/SCAI Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease; see Section 6.2.1, Oral Antiplatelet Therapy.

6.2.1 Oral Antiplatelet Therapy

Continuation of combination treatment with aspirin and a $P2Y_{12}$ inhibitor after PCI appears to reduce major adverse cardiac events. On the basis of randomized clinical trials, the 2016 ACC/AHA guidelines recommend aspirin 81 mg daily be given indefinitely after PCI. In patients who are not at high risk of bleeding, a $P2Y_{12}$ inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in acute coronary syndrome (ACS) patients.

Full guidelines are provided at the following website: http://www.onlinejacc.org

Consistent with the 2016 ACC/AHA guidelines,[1] and the DAPT Study,[2] longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk. In patients who are at a high risk of bleeding or who develop significant bleeding during DAPT treatment, these guidelines suggest that a shorter DAPT duration may be reasonable.

Based upon the results of the EVOLVE Short DAPT Study the SYNERGY stent can be safely used in conjunction with shortened DAPT in patients at high risk for bleeding. In the EVOLVE Short DAPT Study, high bleeding risk subjects were defined as meeting one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL. Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, ischemic and bleeding risks, and patient preference.

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Generally, it is recommended to postpone elective surgery for one year and among those patients for whom surgery cannot be deferred, ASA should be considered during the perioperative period in high risk DES patients.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

[1] Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2016;68:1082 -1115.
[2] Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. N Engl J Med. 2014; 371:2155-66.

6.3 Longitudinal Stent Deformation

Longitudinal stent deformation is a recognized potential failure mode of thin strut coronary stents.[3] Crossing a newly deployed stent with a second device, such as a balloon catheter, stent system or IVUS catheter, can lead to the second device transmitting force to the implanted stent. In this situation, if the second device is advanced or retracted, longitudinal stent deformation (i.e., longitudinal compression or elongation) of the implanted stent may occur. Although a rare event, longitudinal stent deformation may result in adverse clinical events and/or the need for additional treatment including repeat dilation of the implanted stent, placement of a second stent, and/or surgical intervention.

An analysis of complaint reports suggests that coronary artery calcification, vessel tortuosity, and stent malapposition in conjunction with crossing a newly deployed stent with an ancillary device may be associated with an increased risk of longitudinal stent deformation. Implantation techniques that may reduce the likelihood of procedure related complications, including stent deformation, are described in the appropriate sections of this DFU (see sections 14.3.4 Delivery Procedure, 14.3.5 Deployment Procedure, 14.3.6 Removal Procedure and Post-Deployment Dilation of Stented Segment).

[3] Hanratty CG, Walsh SJ. Longitudinal Compression: A "new" Complication with Modern Coronary Stent Platforms - Time to Think Beyond Deliverability? Eurointervention 2011;7:872-877

6.4 Use of Multiple Stents

In the EVOLVE Clinical Program, the protocols specified that lesions were to be treated with no more than one stent, except in situations involving bailout stenting. The use of multiple DES will expose the patient to larger amounts of drug and polymer. When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition to avoid the possibility of corrosion due to the presence of dissimilar metals in a conducting medium. Potential interactions of the SYNERGY Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

6.5 Brachytherapy

The safety and effectiveness of the SYNERGY Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in a SYNERGY Stent have not been established. Both vascular brachytherapy and the SYNERGY Stent alter arterial remodeling. The interaction between these two treatments has not been determined.

6.6 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices or laser angioplasty catheters in conjunction with an implanted SYNERGY Stent have not been established.

6.7 Use in Special Populations

6.7.1 Pregnancy

Pregnancy "Category C". See Section 7.5, Pregnancy. The SYNERGY™ Stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a SYNERGY Stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

There are also potential risks to the fetus due to the ionizing radiation required for visualization during PCI procedures.

6.7.2 Lactation

See Section 7.6, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent for the mother.

6.7.3 Gender

See Clinical Information – Section 10, Clinical Studies. Clinical studies of the SYNERGY Stent were not powered to study safety or effectiveness of the SYNERGY Stent in sex-specific subgroups, however exploratory analyses were performed.

6.7.4 Ethnicity

See Clinical Information – Section 10, Clinical Studies. Clinical studies of the SYNERGY Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity or race, either by individual category or when grouped by Caucasian and non-Caucasian.

6.7.5 Pediatric Use

The safety and effectiveness of the SYNERGY Stent in pediatric patients have not been established.

6.7.6 Geriatric Use

Clinical studies of the SYNERGY Stent did not have an upper age limit. Among the 846/1684 patients treated with the SYNERGY Stent in the EVOLVE II Randomized controlled study, 407 patients were age 65 or older and 46 patients were age 80 or older. A post hoc analysis of patients treated with the SYNERGY Stent showed no significant differences in 12-month clinical outcomes (primary endpoint of target lesion failure) between patients under age 65 and those age 65 or older.

6.8 Lesion/Vessel Characteristics

The safety and effectiveness of the SYNERGY Stent have not been established in the cerebral, carotid, or peripheral vasculature or in the following patient populations:

- Patients with vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameters <2.25 or >5.00 mm.
- Patients with coronary artery lesions longer than 34 mm or requiring more than one SYNERGY Stent.
- Patients with lesions located in saphenous vein grafts, in the left main coronary artery, ostial location, or complex bifurcation (e.g. bifurcation lesion requiring treatment with more than one stent).
- Patients with diffuse disease or reduced blood flow distal to the identified lesions.

- Patients with a recent acute ST elevation myocardial infarction where there is evidence of thrombus or poor flow.
- Patients with in-stent restenosis.
- Patients with a chronic total occlusion.
- Patients with 3 vessel disease.

6.9 Drug Interactions

See Section 7.3, Drug Interactions. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the SYNERGY Stent because of limited systemic exposure to everolimus eluted from SYNERGY Stent used in the EVOLVE clinical trials (see Section 7.2, Pharmacokinetics). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place a SYNERGY Stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a SYNERGY Stent.

6.10 Immune Suppression Potential

Everolimus, the active drug component of the SYNERGY Stent, is an immunosuppressive agent. Immune suppression as a result of everolimus exposure was not observed in the EVOLVE Clinical Program. However, for patients who receive several SYNERGY Stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein.

Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

6.11 Lipid Elevation Potential

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low- and high-dose prolonged oral therapy in a dose-related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the SYNERGY Stent is expected to be significantly lower than concentrations usually obtained in transplant patients.

6.12 Magnetic Resonance Imaging (MRI) Safety Information:

Non-clinical testing has demonstrated that the SYNERGY Stent is MR Conditional for single and overlapped conditions up to 75 mm. A patient with this device can be safely scanned in a Magnetic Resonance system meeting the following conditions:

- 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)

Under the scan conditions defined above, the SYNERGY Stent is expected to produce a maximum temperature rise of 3.1ºC after 15 minutes of continuous scanning.

MR Image quality may be compromised if the area of interest is within the lumen or relatively near the stent. Therefore, it may be necessary to optimize MR imaging parameters for the presence of the stent. The image artifact extends approximately 1 cm from the stent when scanned in non-clinical MR testing specified in ASTM F2119-07. The artifact does obscure the device lumen. Image artifact was minimized using the spin echo sequence versus gradient echo.

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.

Magnetic Resonance Conditional

6.13 Stent Handling (also see Section 14, Operational Instructions)

- For single use only. Do not resterilize or reuse this product. Note product “Use By” date. (see Section 1, Warning)
- The premounted SYNERGY Stent and its delivery system are designed for use as a unit. The stent is not to be removed from its delivery balloon. The stent is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and coating and/or lead to stent embolization.

• Special care must be taken not to handle or in any way disrupt the stent position on the delivery balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guide catheter hub.

• Excessive manipulation or handling may cause coating damage, contamination, or dislodgment of the stent from the delivery balloon.

• Use only the appropriate balloon inflation media (see Section 14.3.3, Balloon Preparation). Do not use air or any gas medium to inflate the balloon.

• In the event the SYNERGY Stent is deployed or damaged, do not use the product and contact your local Boston Scientific Representative for return information.

6.14 Stent Placement

Preparation

• Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 14.3.3, Balloon Preparation.

•The vessel should be pre-dilated with an appropriately sized balloon. Failure to do so may increase the risk of placement difficulty and procedural complications

• If unusual resistance is felt at any time during lesion access before stent implantation, see Section 6.15, Stent Delivery System Removal.

• An unexpanded stent should be introduced into the coronary arteries one time only. An unexpanded stent should not be subsequently moved in and out through the distal end of the guide catheter as stent or coating damage or stent dislodgment from the balloon may occur.

Placement

• Do not expand the stent if it is not properly positioned in the vessel (see Section 6.15, Stent Delivery System Removal).

• Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Section 14.4, In Vitro Information, Table 14.1, Typical SYNERGY Stent System Compliance). Use of pressures higher than specified on product label may result in a ruptured balloon and intimal damage and dissection.

• The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.

• Stent placement may potentially compromise side branch patency.

• Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, repeat dilation, placement of additional stents, or other).

• When treating multiple lesions, the distal lesion should generally be stented first, followed by stenting of the more proximal lesion(s). Stenting in this order alleviates the need to cross the proximal stent in placement of the distal stent and reduces the chances of dislodging or damaging the proximal stent.

6.15 Stent Delivery System Removal

• Following stent placement confirm complete balloon deflation. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.

• If unusual resistance is felt at any time during lesion access before stent implantation, the stent delivery system and the guide catheter should be removed as a single unit.

• Retraction of an unexpanded stent back into the guide catheter could result in stent or coating damage or stent dislodgment from the balloon. If retraction of the unexpanded stent back into the guide catheter is required, ensure the guide catheter is coaxially aligned with the stent system and cautiously withdraw the stent system into the guide catheter under direct fluoroscopic visualization.

• Stent retrieval methods (use of additional wires, snares and/ or forceps) may result in additional trauma to the vascular access site. Complications can include bleeding, hematoma, or pseudoaneurysm.

Note: When removing the entire stent delivery system and guide catheter as a single unit, the following steps should be executed under direct fluoroscopic visualization.

• If greater than usual resistance is felt during delivery system withdrawal, pay particular attention to guide catheter position. In some cases, it may be necessary to pull back slightly on the guide catheter in order to prevent deep seating (unplanned advancement) of the guide catheter and subsequent vessel damage. In cases where planned guide catheter movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure there is no damage to the coronary vasculature.

• Following stent placement confirm complete balloon deflation. Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 30 seconds, for balloon deflation. Larger and longer balloons may require more time for deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.

• Maintain guidewire placement across the lesion during the entire removal process. Carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is just distal to the guide catheter distal tip.

• The stent delivery system and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten. Carefully retract the stent delivery system into the guide catheter and remove the stent delivery system and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion.

Failure to follow these steps, and/or applying excessive force to the stent delivery system, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery system.

6.16 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- In the EVOLVE Clinical program, a $P2Y_{12}$ inhibitor was administered pre-procedure and for a period of 6 months post-procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with a $P2Y_{12}$ inhibitor and then continued indefinitely to reduce the risk of thrombosis. See Section 10, Clinical Studies, for more specific information.
- If the patient requires MRI imaging, see Section 6.12, Magnetic Resonance Imaging (MRI).

7 DRUG INFORMATION

7.1 Mechanism of Action

The mechanism by which the SYNERGY™ Stent inhibits neointimal growth as seen in pre-clinical studies has been established.[4] At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

[4] Lavigne, MC, Grimsby, JL, Eppihimer, MJ. J Cardiovasc Pharmacol. 2012;59:165-174

7.2 Pharmacokinetics

Everolimus Pharmacokinetics (PK) when eluted from the SYNERGY Stent post-implantation has 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. Whole blood everolimus PK parameters determined from patients receiving the SYNERGY Stent are provided in Table 7.1.

Table 7.1 Whole Blood Everolimus Pharmacokinetic Parameters (Mean ± SD) for SYNERGY (Groups with Three or More Patients) Following SYNERGY Stent Implantation.

Pharmacokinetic Parameter**	All Subjects		
	58 µg [b]	113 µg [c]	189 µg
N	3 [c]	3 [b]	4 [b]
t_{max} (h)	0.90 ± 0.36	0.48 ± 0.08	0.48 ± 0.03
C_{max} (ng/mL)	0.31 ± 0.07	0.35 ± 0.04	0.84 ± 0.41
AUC_{0-t} (ng•h/mL)	0.32 ± 0.25	0.56 ± 0.47	8.50 ± 3.91
AUC_{0-24h} (ng•h/mL)	0.32 ± 0.25	0.56 ± 0.47	6.73 ± 2.10
$AUC_{0-\infty}$ [a] (ng•h/mL)	NA	NA	47.81 ± 61.50
$t_{1/2term}$ [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
[a]: Accurate determination not possible
[b]: n=0 for $AUC_{0-\infty}$, $t_{1/2\ term}$ and CL
[c]: n=1 for $AUC_{0-\infty}$, $t_{1/2\ term}$ and CL
t_{max} (h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
AUC_{0-24h} = the area beneath the blood concentration versus time curve: time zero to 24 hours post-implant
$AUC_{0-\infty}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance
**Dose-normalized C_{max} and AUC_{0-24h} were plotted versus total dose. Across the dose range (58 to 257 µg), the plots showed that the data from the individual subjects are evenly distributed around the median values.

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 $t_{1/2\ term}$ and $AUC_{0-\infty}$ 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 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.

7.3 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 SYNERGY Stent because of limited systemic exposure to everolimus eluted from SYNERGY (see Section 6.9, Drug Interactions and Section 7.2, Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the SYNERGY Stent in a patient taking a drug with known interaction with everolimus.

The amount of drug that circulates in the bloodstream following implantation of a SYNERGY Stent is significantly lower than that obtained with oral doses. Everolimus, when prescribed as an oral medication, in systemic doses, may interact with the drugs/foods listed below. Medications that are strong inhibitors of CYP3A4 or PgP might reduce everolimus metabolism in vivo. Hence, co-administration of strong inhibitors of CYP3A4 or PgP may increase the blood concentrations of everolimus.

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

Zortress™, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day. Outside the U.S., Zortress is sold under the brand name, Certican™, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor™ for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the

bloodstream following implantation of a SYNERGY Stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day), see Section 7.2, Pharmacokinetics.

7.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

SYNERGY Stent is made of platinum chromium alloy which consists of platinum, chromium, iron, nickel, and molybdenum, and contains the drug everolimus in a similar amount as PROMUS™ (XIENCE V™). Therefore, the previous testing conducted on such devices is also applicable for SYNERGY as described below.

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of PROMUS (XIENCE V) everolimus eluting stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group PROMUS (XIENCE V) Stent. The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group.

Based on the results of this study, the PROMUS (XIENCE V) Stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

SYNERGY Stent was evaluated for genotoxicity using Ames bacterial mutagenicity assay, in vitro gene mutation assay in mammalian cells (mouse lymphoma) at thymidine kinase loci and mouse bone marrow micronucleus assay. The results from these in vitro and in vivo studies showed that SYNERGY Stents are not mutagenic and non-genotoxic in nature. In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of PROMUS (XIENCE V) Stent in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. There was no statistical difference between the test article PROMUS (XIENCE V) Stent and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in-utero mortality. Additionally, the PROMUS (XIENCE V) Stent did not cause any reproductive toxicity in the offspring in this study.

The SYNERGY Stent also has a bioabsorbable polymer coating PLGA which is known to degrade by hydrolysis into lactic and glycolic acid and ultimately metabolized into carbon dioxide and water. PLGA is being used as part of medical devices and also as a drug delivery agent for many years. There are no known genotoxic, carcinogenic or reproductive toxicity effects of PLGA in published literature.

7.5 Pregnancy

Pregnancy “Category C”: There are no everolimus or SYNERGY Stent related studies in pregnant women. Effects of a similar stent (PROMUS/XIENCE V) on prenatal and postnatal rat development were not different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential

Effective contraception should be initiated before implanting a SYNERGY Stent and continued for one year post-implantation. The SYNERGY Stent should be used in pregnant women only if the potential benefits justify the potential risks.

Safety of the SYNERGY Stent has not been evaluated in males intending to father children.

7.6 Lactation

It is not known whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to SYNERGY™ Stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternative percutaneous coronary intervention procedure.

8 OVERVIEW OF CLINICAL STUDIES

The principal safety and effectiveness for the SYNERGY Stent System is derived from the global EVOLVE Clinical Trial Program, a series of clinical trials conducted on the SYNERGY Stent System.

The EVOLVE 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 (First Human Use) trial and the EVOLVE II study, which comprises a 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. Following commercialization, post-market clinical studies have been conducted to evaluate shortened dual antiplatelet therapy following SYNERGY stent implantation in specific patient subsets. The EVOLVE Short DAPT Study was conducted to evaluate the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent System. A summary of the EVOLVE, EVOLVE II RCT, PK, DM, QCA and EVOLVE Short DAPT trial designs are presented in Table 8.1.

8.1 EVOLVE Clinical Trial

EVOLVE is a prospective, randomized, multi-center single blind non-inferiority study designed to evaluate clinical, angiographic and IVUS outcomes for the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System compared to PROMUS Element™ Stent in the treatment of subjects with atherosclerotic lesions ≤28 mm

in length (by visual estimate) in *de novo* coronary arteries ≥2.25 mm to ≤3.50 mm in diameter (by visual estimate).

The primary clinical endpoint was the 30-day target lesion failure (TLF) rate defined as a composite of cardiac death or myocardial infarction (MI) related to the target vessel, or ischemia-driven target lesion revascularization (TLR). The primary angiographic endpoint was in-stent late loss as measured by QCA at 6 months.

A total of 291 patients were enrolled at 29 sites in Europe and Asia-Pacific region (Australia and New Zealand). The protocol mandated antiplatelet therapy compliance in accordance with the 2007 ACC/AHA/SCAI Guidelines for PCI.[5]

The study is now complete including follow-up through 5 years.

[5] King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. Circulation. 2008; 117:261–295.

8.2 EVOLVE II Clinical Trial

8.2.1 Randomized Controlled Trial (RCT)

The EVOLVE II RCT is a prospective, randomized (1:1), controlled, single-blind, multi-center, 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. To be eligible for enrollment, patients had to have silent ischemia, stable angina, unstable angina or non-ST elevation myocardial infarction (NSTEMI); ST elevation MI (STEMI) was an exclusion criterion. Predilation was required by the study protocol, patients pre-treated with rotational or directional atherectomy or cutting/scoring balloons were eligible for enrollment. Patients with bifurcation lesions where treatment with a single stent was planned were eligible while those with bifurcation lesions where treatment with two stents was planned were not eligible. Saphenous vein graft lesions, in-stent restenosis and lesions in the left main coronary artery were also excluded.

The primary endpoint was the rate of TLF, defined as any ischemia-driven TLR, MI 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.

A total of 1684 patients (846 SYNERGY Stent and 838 PROMUS Element Plus Stent) were randomized and enrolled at 125 sites in 16 countries in the Asia-Pacific region, Europe, Japan, Canada and the United States. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/SCAI Guidelines for PCI.[6]

The study is now complete including follow-up through 5 years.

[6] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651.

8.2.2 Pharmacokinetics (PK) Sub-study

EVOLVE II PK is a prospective, single-arm, multi-center, observational sub-study of the EVOLVE II Trial to evaluate everolimus blood levels following stent implantation in patients who undergo treatment with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System.

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. A total of 21 patients were enrolled at 2 sites in the United States and 4 sites in Japan. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/ SCAI Guidelines for PCI.[7] Clinical follow-up is complete through 5 years. See Section 7.2, Pharmacokinetics.

[7] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651.

8.2.3 Diabetic (DM) Sub-study

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 Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of coronary lesions in patients with medically treated diabetes mellitus. 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.
The primary endpoint was the rate of TLF at 12 months post-index procedure, compared to a performance goal based on historical everolimus-eluting stent results based on subjects with diabetes.

The EVOLVE II DM sub-study pooled: 1) diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patients) with 2) diabetic subjects enrolled in the non-randomized Diabetes single-arm study (203 patients from 48 sites in Asia-Pacific region, Europe, Canada and the United States), following completion of EVOLVE II RCT enrollment. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/SCAI Guidelines for PCI.[8]

The sub-study is now complete including follow-up thorough 5 years.

[8] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011;124:e574-e651

8.3 EVOLVE II Quantitative Coronary Angiography (QCA) Trial

EVOLVE II QCA is a prospective, single-arm, multi-center, observational study designed to evaluate clinical, angiographic and IVUS outcomes in atherosclerotic coronary lesions treated with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. Patients with 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. The primary endpoint was in-stent late loss at 9 months post-procedure as measured by quantitative coronary angiography (QCA). All patients were required to undergo 9 month angiography and IVUS assessments. The 9 month in-stent late loss performance goal was based on historical PLATINUM QCA and the PROMUS arm of RESOLUTE all-comers results.

A total of 100 patients were enrolled at 12 sites in Australia, Japan, New Zealand, and Singapore. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/ SCAI Guidelines for PCI.[9] The study is complete.

[9] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

8.4 EVOLVE Short DAPT Study

The EVOLVE Short DAPT Study* is a prospective, multi-center, single-arm study in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent. A historical control and a propensity score approach was used to assess the safety of 3-month DAPT in high bleeding risk patients. High bleeding risk subjects were enrolled if they met one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL. Subjects were prescribed dual antiplatelet therapy ($P2Y_{12}$ inhibitor + aspirin) between 0-3 months post-procedure. Aspirin was optional between 0-3 months for subjects on chronic anticoagulation. Subjects were eligible to discontinue $P2Y_{12}$ inhibitor at 3 months if they were compliant with the prescribed dual antiplatelet therapy and were free from events between 0-3 months (stent thrombosis, myocardial infarction, revascularization, or stroke). Subjects that discontinued $P2Y_{12}$ inhibitor at 3-months were prescribed aspirin through the end of study. The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or MI, and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis related to SYNERGY. The pre-specified secondary endpoint was the rate of BARC 2,3,5 Bleeding** between 3-15 months. A total of 2,009 patients were enrolled at 110 sites in the United States, Europe, Brazil and Japan, of which 1,487 patients were eligible to and discontinued $P2Y_{12}$ inhibitor at 3-months. Patients were followed at 3, 6, 12- and 15-months post-index procedure. The study is considered complete with follow-up through 15-months.

* Mauri L, Kirtane AJ, Windecker S, et al. Am Heart J. 2018;205:110–117.

**Mehran R, Rao SV, Bhatt DL et al. Circulation 2011;123:2736-2747.

Table 8.1 Comparison of Clinical Studies involving the SYNERGY Stent

	EVOLVE	EVOLVE II				EVOLVE Short DAPT Study
		RCT	DM	PK	QCA	
Purpose	Evaluation of safety and effectiveness in native *de novo* coronary lesions	Evaluation of safety and effectiveness in native coronary lesions	Evaluation of safety and effectiveness in native coronary lesions in patients with medically treated diabetes mellitus	Evaluation of everolimus blood levels	Evaluation of angiographic and IVUS outcomes in native coronary lesions	Evaluation of safety of 3-month DAPT in subjects at high risk for bleeding** receiving SYNERGY
Study Design	Prospective, randomized, controlled, multi-center, single-blind non-inferiority to PROMUS Element™	Prospective, randomized, controlled, multi-center, single-blind non-inferiority to PROMUS Element™ Plus	Prospective, single arm, multi-center, comparison to performance goal	Prospective, single arm, multi-center, observational study	Prospective, single arm, multi-center, observational; study	Prospective, multi-center, single arm, historical control, propensity score approach
Primary Endpoint(s)	30 Day TLF 6 month In-stent late loss	12-month TLF	12-month TLF	N/A, observational	9 month in-stent late loss	Co-Primary Endpoints (3-15 months): 1,) death/MI; 2.) ARC definite/probable ST related to SYNERGY
Number of Patients (ITT)	291 SYNERGY™ Full dose: 94 SYNERGY ½ dose: 99 PROMUS Element: 98	1684 SYNERGY: 846 PROMUS Element Plus: 838	203 SYNERGY	21 SYNERGY	100 SYNERGY	2,009 SYNERGY
Lesion Criteria: Vessel Diameter (by visual estimate), mm	≥2.25 to ≤3.50	≥2.25 to ≤4.00				No Restriction
Lesion Criteria: Lesion Length (by visual estimate), mm	≤28	≤34				No Restriction
Total Target Lesions	1	Up to 3 in 2 epicardial vessels				

Stent Matrix, mm	Diameter: 2.25, 2.50, 2.75, 3.00, 3.50 Length: 8, 20, 32	Diameter: 2.25, 2.50, 3.00, 3.50, 4.00 Length: 8, 12, 20, 28, 32/38*		
Post-Procedure Antiplatelet Therapy	A thienopyridine for at least 6 months, ideally for 12 months in patients who were not at high risk of bleeding. ASA: indefinitely	A $P2Y_{12}$ inhibitor for at least 6 months, ideally for 12 months in patients who were not at high risk of bleeding. ASA: indefinitely		$P2Y_{12}$ inhibitor + ASA for 3-months, then ASA 3-15 months. For subjects on anticoagulation, ASA option 0-3 months.
Follow-Up	Clinical: 30 days, 6 months, 9 months 1 year, annually 2 – 5 years Angiographic: 6 months IVUS: 6 months	Clinical: 30 days, 6 months, 1 year, 18 months, annually 2 – 5 years	Clinical: 30 days, 9 months, 1 year, Angiographic: 9 month, IVUS: 9 month	Clinical: 3 months, 6 months, 1 year and 15 months
	* 2.25 x 38 mm is only available in the SYNERGY test matrix and 2.25 x 32 is only available in the PROMUS Element Plus control matrix. **In the EVOLVE Short DAPT Study, high bleeding risk subjects were defined as meeting one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL Abbreviations: ASA=aspirin; BMS=bare-metal stent; DAPT=dual antiplatelet therapy; DM=diabetes mellitus; IVUS=intravascular ultrasound; MI=myocardial infarction; PK=pharmacokinetics; PLGA; QCA=quantitative coronary angiography; RCT=randomized controlled trial; TLF=target lesion failure; TLR=target lesion revascularization			

9 ADVERSE EVENTS:

9.1 Observed Adverse Events

Observed adverse event experience comes from the EVOLVE, EVOLVE II (RCT), EVOLVE II DM, EVOLVE II QCA, and the EVOLVE Short DAPT Study. Major clinical events for these studies are shown in Table 9.1.

Table 9.1 EVOLVE II RCT and DM Sub-study Major Clinical Events From Post-Procedure to 5 year, EVOLVE II QCA Major Clinical Events From Post-Procedure to 9 month Follow-Up, and EVOLVE From Post-Procedure to 5 year Follow-Up, and EVOLVE Short DAPT Study to 15-Month Follow-up.

	EVOLVE II RCT		EVOLVE II DM	EVOLVE II QCA	EVOLVE	EVOLVE Short DAPT Study		
	SYNERGY™ (N=846)*	PROMUS Element™ Plus[1] (N=838)*	SYNERGY (N=466)*	SYNERGY (N=100)*	SYNERGY (N=94)*	SYNERGY (N=2,009)	3-Month DAPT SYNERGY (N=1,487)	Non 3-Month DAPT SYNERGY (N=522)
In-Hospital All death, MI, TVR	3.9% (33/846)	3.9% (33/838)	3.2% (15/466)	5.0% (5/100)	1.1% (1/94)	0.5 (10/2009)**	0.0% (0/1487)****	1.9% (10/522)****
All Death	0.0% (0/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.1% (3/2009)	0.0% (0/1487)	0.6% (3/522)
Cardiac Death	0.0% (0/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.1% (2/2009)	0.0% (0/1487)	0.4% (2/522)
Non-cardiac Death	0.0% (0/846)	0.0% (0/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
MI	3.5% (30/846)	3.8% (32/838)	3.0% (14/466)	5.0% (5/100)	1.1% (1/94)	0.4% (9/2009)	0.0% (0/1487)	1.7% (9/522)
Q-Wave MI	0.1% (1/846)	0.0% (0/838)	0.4% (2/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
Non-Q-Wave MI	3.4% (29/846)	3.8% (32/838)	2.6% (12/466)	5.0% (5/100)	1.1% (1/94)	0.4% (9/2009)	0.0% (0/1487)	1.7% (9/522)
Cardiac death or MI	3.5% (30/846)	3.8% (32/838)	3.0% (14/466)	5.0% (5/100)	1.1% (1/94)	0.5% (10/2009)	0.0% (0/1487)	1.9% (10/522)
TVR	0.5% (4/846)	0.1% (1/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
TLR	0.4% (3/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
Non-TLR	0.1% (1/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
30-Day All death, MI, TVR	4.3% (36/846)	5.0% (42/833)	3.9% (18/466)	5.0% (5/100)	1.1% (1/93)	1.4% (27/1995)**	0.0% (0/1487)****	5.3% (27/508)****
9 month All death, MI, TVR				8.0% (8/100)	5.4% (5/93)			
All Death				0.0% (0/100)	1.1% (1/93)			
Cardiac Death				0.0% (0/100)	0.0% (0/93)			
Non-cardiac Death				0.0% (0/100)	1.1% (1/93)			
MI				5.0% (5/100)	1.1% (1/93)			
Q-Wave MI				0.0% (0/100)	0.0% (0/93)			
Non-Q-Wave MI				5.0% (5/100)	1.1% (1/93)			
TVR				3.0% (3/100)	3.2% (3/93)			
TLR				1.0% (1/100)	1.1% (1/93)			
Non-TLR				2.0% (2/100)	2.2% (2/93)			
1-Year All death, MI, TVR	9.3% (77/832)	8.4% (68/808)	9.7% (44/455)		7.6% (7/92)	6.9% (133/1938)**	3.8% (56/1473)****	16.6% (77/465)****
All Death	1.1% (9/832)	1.1% (9/808)	1.3% (6/455)		2.2% (2/92)	4.9% (94/1938)	2.8% (41/1473)	11.4% (53/465)
Cardiac Death	0.5% (4/832)	0.9% (7/808)	0.7% (3/455)		0.0% (0/92)	2.6% (51/1938)	1.4% (20/1473)	6.7% (31/465)
Non-cardiac Death	0.6% (5/832)	0.2% (2/808)	0.7% (3/455)		2.2% (2/92)	1.8% (34/1938)	1.3% (19/1473)	3.2% (15/465)
MI	5.4% (45/832)	5.0% (40/808)	5.9% (27/455)		3.3% (3/92)	2.9% (56/1938)	1.4% (20/1473)	7.7% (36/465)

Q-Wave MI	0.2% (2/832)	0.2% (2/808)	0.4% (2/455)		0.0% (0/92)	0.2% (3/1938)	0.1% (2/1473)	0.2% (1/465)
Non-Q-Wave MI	5.2% (43/832)	4.7% (38/808)	5.5% (25/455)		3.3% (3/92)	2.8% (54/1938)	1.3% (19/1473)	7.5% (35/465)
TVR	3.8% (32/832)	3.6% (29/808)	5.3% (24/455)		3.3% (3/92)	2.4% (46/1938)	1.8% (26/1473)	4.3% (20/465)
TLR	2.6% (22/832)	1.7% (14/808)	4.4% (20/455)		1.1% (1/92)	1.5% (30/1938)	1.2% (17/1473)	2.8% (13/465)
Non-TLR	1.8% (15/832)	2.2% (18/808)	1.8% (8/455)		2.2% (2/92)	1.2% (23/1938)	0.8% (12/1473)	2.4% (11/465)
15-Month All death, MI, TVR						8.7% (166/1915)**	5.4% (79/1461)****	19.2% (87/454)****
All Death						6.1% (117/1915)	4.2% (61/1461)	12.3% (56/454)
Cardiac Death						3.2% (62/1915)	2.0% (29/1461)	7.3% (33/454)
Non-cardiac Death						2.2% (43/1915)	1.8% (27/1461)	3.5% (16/454)
MI						3.5% (67/1915)	1.8% (26/1461)	9.0% (41/454)
Q-Wave MI						0.2% (3/1915)	0.1% (2/1461)	0.2% (1/454)
Non-Q-Wave MI						3.4% (65/1915)	1.7% (25/1461)	8.8% (40/454)
TVR						3.2% (62/1915)	2.6% (38/1461)	5.3% (24/454)
TLR						2.2% (43/1915)	1.8% (27/1461)	3.5% (16/454)
Non-TLR						1.5% (29/1915)	1.1% (16/1461)	2.9% (13/454)
2-Year All death, MI, TVR	12.8% (105/823)	11.7% (93/797)	14.7% (66/450)		8.7% (8/92)			
3-Year All death, MI, TVR	15.5% (127/819)	14.6% (114/783)	17.5% (78/445)		9.8% (9/92)			
4 -Year All death, MI, TVR	19.2% (156/811)	18.8% (148/787)	21.4% (96/448)		9.8% (9/92)			
5-Year All death, MI, TVR	22.6% (182/807)	22.4% (175/781)	26.7% (119/446)		10.5% (9/86)			
All Death	6.9% (56/807)	7.4% (58/781)	10.3% (46/446)		7.0% (6/86)			
Cardiac Death	3.5% (28/807)	4.2% (33/781)	4.3% (19/446)		1.2% (1/86)			
Non-cardiac Death	3.5% (28/807)	3.2% (25/781)	6.1% (27/446)		5.8% (5/86)			
MI	10.2% (82/807)	9.0% (70/781)	11.2% (50/446)		3.5% (3/86)			
Q-Wave MI	0.4% (3/807)	0.5% (4/781)	0.7% (3/446)		0.0% (0/86)			
Non-Q-Wave MI	9.9% (80/807)	8.5% (66/781)	10.8% (48/446)		3.5% (3/86)			
TVR	11.9% (96/807)	11.1% (87/781)	14.8% (66/446)		3.5% (3/86)			
TLR	6.7% (54/807)	5.2% (41/781)	9.0% (40/446)		1.2% (1/86)			
Non-TLR	6.7% (54/807)	7.7% (60/781)	9.0% (40/446)		2.3% (2/86)			
In-Hospital ARC Stent Thrombosis								
Definite or Probable	0.2% (2/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
Definite	0.2% (2/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)

Probable	0.0% (0/846)	0.0% (0/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
30-Day ARC Stent Thrombosis								
Definite or Probable	0.4% (3/846)	0.6% (5/833)	1.1% (5/466)	0.0% (0/100)	0.0% (0/93)	0.2% (4/1995)	0.0% (0/1487)	0.8% (4/508)
Definite	0.2% (2/846)	0.2% (2/833)	1.1% (5/466)	0.0% (0/100)	0.0% (0/93)	0.1% (1/1995)	0.0% (0/1487)	0.2% (1/508)
Probable	0.1% (1/846)	0.4% (3/833)	0.0% (0/466)	0.0% (0/100)	0.0% (0/93)	0.2% (3/1995)	0.0% (0/1487)	0.6% (3/508)
9-Month ARC Stent Thrombosis								
Definite or Probable				0.0% (0/100)	0.0% (0/92)			
Definite				0.0% (0/100)	0.0% (0/92)			
Probable				0.0% (0/100)	0.0% (0/92)			
1-Year ARC Stent Thrombosis								
Definite or Probable	0.4% (3/832)	0.6% (5/808)	1.1% (5/455)		0.0% (0/91)	0.4% (8/1938)	0.1% (2/1473)	1.3% (6/465)
Definite	0.2% (2/832)	0.2% (2/808)	1.1% (5/455)		0.0% (0/91)	0.3% (5/1938)	0.1% (2/1473)	0.6% (3/465)
Probable	0.1% (1/832)	0.4% (3/808)	0.0% (0/455)		0.0% (0/91)	0.2% (3/1938)	0.0% (0/1473)	0.6% (3/465)
15-Month ARC Stent Thrombosis								
Definite or Probable						0.4% (8/1915)	0.1% (2/1461)	1.3% (6/454)
Definite						0.3% (5/1915)	0.1% (2/1461)	0.7% (3/454)
Probable						0.2% (3/1915)	0.0% (0/1461)	0.7% (3/454)
2-Year ARC Stent Thrombosis								
Definite or Probable	0.4% (3/823)	0.8% (6/797)	1.1% (5/450)		0.0% (0/92)			
3-Year ARC Stent Thrombosis								
Definite or Probable	0.5% (4/819)	0.8% (6/783)	1.1% (5/445)		0.0% (0/92)			
4-Year ARC Stent Thrombosis								
Definite or Probable	0.6% (5/811)	0.9% (7/787)	1.1% (5/448)		0.0% (0/92)			
5-Year ARC Stent Thrombosis								
Definite or Probable	0.7% (6/807)	0.9% (7/781)	1.1% (5/446)		0.0% (0/80)			

[1] DES Control

Numbers are % (count/sample size).

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2- 5 year clinical outcomes are based on the safety population only including patients who received a study stent.

** MACE defined as Cardiac Death, MI, TVR in EVOLVE Short DAPT Study

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

The EVOLVE II definition for MI was as follows:

- Peri-procedural MI:
  i) Development of new pathological Q-waves or
  ii) Elevation of CK-MB levels >3x ULN, or if CKMB is not performed total CK must be >2x ULN, or if Troponin was only available enzyme, it must be >3x ULN. There must also be no evidence of pre-procedure biomarker elevations, or one of the following must be true: ≥50% increase in cardiac biomarker result, or evidence that cardiac biomarker values were decreasing prior to suspected MI or
  iii) Autopsy evidence of acute MI
- Spontaneous MI definition: Detection of rise and/or fall of CK-MB or Troponin with at least one value above 99th percentile of ULN, together with evidence of myocardial ischemia and at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, development of new pathological Q-waves, imaging evidence of new loss of myocardium or new regional wall abnormality.

The EVOLVE definition for MI was as follows:

- Peri-procedural Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK-MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1× >ULN and the baseline level must have been <ULN.
- Peri-procedural Non-Q-wave MI: Elevation of CK levels >3x ULN without the presence of new Q-waves, If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >3x ULN and the baseline level must have been <ULN. There must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
- Spontaneous Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1x >ULN and the baseline level must have been <ULN.
- Spontaneous Non-Q-wave MI: De novo elevation of CK levels >2x ULN, without presence of new Q waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >2x ULN and the baseline level must have been <ULN and there must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

The EVOLVE Short DAPT Study used the 3rd Universal Definition of MI*:

<u>Spontaneous MI:</u>

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

<u>Percutaneous Coronary Intervention-Related Myocardial Infarction</u>

Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn value (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

AND

One of the following:

- Symptoms suggestive of myocardial ischemia
- New ischemic ECG changes
- Angiographic findings consistent with a procedural complication
- Imaging demonstrating new loss of viable myocardial or new regional wall motion abnormality are required.

<u>Coronary Artery Bypass Grafting-Related Myocardial Infarction</u>

Coronary artery bypass graft (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL).

AND

One of the following:

- New pathological Q waves or new LBBB
- Angiographically documented new graft or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac marker values would be increased.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

*Thygesen K, Alpert JS, Jaffe AS et al. Journal of the American College of Cardiology 2012;60:1581-1598.

9.2 Potential Adverse Events

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
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation ventricular tachycardia and heart block
- Cardiogenic shock/pulmonary edema
- Death
- Embolization, (air, tissue or thrombotic material or material from device(s) used in the procedure) including stent embolization or migration
- Heart failure
- Hemorrhage, which may require transfusion; including bleeding and hematoma
- Hypotension/hypertension
- Infection, local or systemic; including fever and pyrogen reaction
- Myocardial ischemia or infarction
- Pain, chest or access site
- Pericardial effusion or cardiac tamponade
- Renal insufficiency or failure
- Respiratory failure
- Restenosis or aneurysm of stented segment
- Stent deformation, collapse, or fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Vessel trauma requiring surgical repair or reintervention, including coronary, femoral or radial artery spasm, dissection; occlusion, perforation, rupture, or pseudoaneurysm.

Zortress™, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day. Outside the U.S., Zortress is sold under the brand name, Certican™, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor™ for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses listed above. The amount of drug that circulates in the bloodstream following implantation of a SYNERGY™ Stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day, see Section 7.2, Pharmacokinetics).

- Abdominal pain

- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of 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)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor

- Upper respiratory tract infection
- Urinary tract infection
- Vomiting

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

10 CLINICAL STUDIES

10.1 EVOLVE Trial

Primary Objective: The primary objective of the EVOLVE Clinical Trial was to assess the safety and performance of the SYNERGY Everolimus-Eluting Coronary Stent System for the treatment of subjects with a *de novo* atherosclerotic lesion of up to 28 mm in length (by visual estimate) in a native coronary artery 2.25 mm to 3.50 mm in diameter (by visual estimate) compared to PROMUS Element™.

Design: EVOLVE is a prospective, single arm, randomized, multicenter, single blind non-inferiority study. Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia and a left ventricular ejection fraction (LVEF) ≥30%. Patients with stable angina, unstable angina, or silent ischemia were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. The primary clinical endpoint was the 30-day TLF rate defined as a composite of cardiac death or MI related to the target vessel or TLR. The primary endpoint was the 30-day TLF rate defined as a composite of cardiac death or MI related to the target vessel, or TLR. The primary angiographic endpoint was in-stent late loss as measured by QCA at 6 months. A total of 291 patients were enrolled at 29 sites in Europe and Asia-Pacific region (Australia and New Zealand). The protocol mandated antiplatelet therapy compliance in accordance with the 2007 ACC/AHA/SCAI Guidelines for PCI.[10]

The study is now complete including follow-up through 5 years.

Follow-up included a clinical assessment at 30 days, 6, 9 and 12 months, and 2, 3, 4 and 5 years post index procedure and QCA and IVUS measurements at 6 months. Results are presented in Table 10.1.1.

Demographics: The average patient age was 64.89±11.03 years. Approximately 70% of patients were male, and 17 % of patients had medically treated diabetes.

Baseline lesion characteristics: By QCA, mean reference vessel diameter (RVD) was 2.60±0.45 mm. Mean lesion length was 13.41±6.29 mm. Diameter stenosis was 73.95 ± 10.37%, and over 56.0 % of treated lesions were type B2/C.

[10] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions.

30-Day and 5 year Clinical Outcomes

Table 10.1.1. EVOLVE SYNERGY™ Arm Clinical Results

Parameter	**SYNERGY (N=94*) ITT population**	
Primary clinical endpoint (30 day TLF)	1.1% (1/92)	
Primary angiographic endpoint (6 month in-stent late loss (mm))	0.10±0.25	
Clinical endpoints**	**30 day (ITT population) (N=94*)**	**5 year (Safety population) (N=92*)**
All death, MI, TVR	1.1% (1/93)	10.5% (9/86)
All death or MI	1.1% (1/93)	7.0% (6/86)
All death	0.0% (0/93)	7.0% (6/86)
Cardiac death	0.0% (0/93)	1.2% (1/86)
Non-cardiac death	0.0% (0/93)	5.8% (5/86)

MI***	1.1% (1/93)	3.5% (3/86)
Q-wave MI	0.0% (0/93)	0.0% (0/86)
Non–Q-wave MI	1.1% (1/93)	3.5% (3/86)
TVR, overall	0.0% (0/93)	3.5% (3/86)
TLR, overall	0.0% (0/93)	1.2% (1/86)
Non-TLR TVR, overall	0.0% (0/93)	2.3% (2/86)
Cardiac death or MI	1.1% (1/93)	4.8% (4/84)
TLF	1.1% (1/93)	6.0% (5/84)
TVF	1.1% (1/93)	8.3% (7/84)
ARC ST (definite/probable)	0.0% (0/93)	0.0% (0/80)
Peri-procedural endpoints	**SYNERGY (N=94*) ITT population**	
Clinical procedural success	98.9% (92/93)	
Quantitative coronary angiography		
Pre-procedure		
Lesion length (mm)	13.41±6.29	
Reference vessel diameter (mm)	2.60±0.45	
MLD, in-lesion (mm)	0.68±0.30	
Diameter stenosis (%)	73.95±10.37	
Acute gain, in-stent (mm)	1.83±0.39	
Acute gain, in-segment (mm)	1.46±0.44	
Post Procedure and 6 month		
MLD, in-stent (mm)		
Post-procedure	2.51±0.37	
6 months	2.41±0.42	
MLD, in-segment (mm)		
Post-procedure	2.14±0.41	
6 months	2.06±0.45	
Diameter stenosis, in-stent (%)		
Post-procedure	3.23±9.62	
6 months	6.59±9.90	
Diameter stenosis, in-segment (%)		
Post-procedure	18.06±8.46	
6 months	20.33±10.96	
Intravascular ultrasound		
Incomplete stent apposition		

Post-procedure	0.0% (0/78)
6 months	4.2% (3/71)
Vessel area (mm^2)	
Post-procedure	14.06±4.05
6 months	14.51±4.48
Stent area (mm^2)	
Post-procedure	7.17±1.96
6 months	7.03±2.10
Lumen area (mm^2)	
Post-procedure	7.17±1.96
6 months	6.86±2.11
Vessel volume (mm^3)	
Post-procedure	341.87±149.61
6 months	344.73±153.08
Stent volume (mm^3)	
Post-procedure	175.19±77.73
6 months	169.91±75.85
Lumen volume (mm^3)	
Post-procedure	175.19±77.73
6 months	164.22±75.86
In-stent net volume obstruction (%)	
Post-procedure	0.00±0.00
6 months	2.68±4.60

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2 - 5 year clinical outcomes are based on the safety population only including patients who received a study stent.
Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
MLD=minimum lumen diameter.

**Data presented are for full dose SYNERGY Stent.

*** MI rates based on EVOLVE MI Definition:

- Peri-procedural Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1×>ULN and the baseline level must have been <ULN.
- Peri-procedural Non-Q-wave MI: Elevation of CK levels >3x ULN, without the presence of new Q-waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >3x ULN and the baseline level must have been <ULN and there must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
- Spontaneous Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1 x >ULN and the baseline level must have been <ULN.
- Spontaneous Non-Q-wave MI: De novo elevation of CK levels >2x ULN, without presence of new Q waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >2x ULN and

the baseline level must have been <ULN and there must also be anyone of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality it must be >2x ULN and the baseline level must have been <ULN and there must also be anyone of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

10.2 EVOLVE II Randomized Controlled Trial (RCT)

Primary Objective: The primary objective of the EVOLVE II RCT was 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 atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[11] Patients could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was the rate of target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion (TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death, at 12 months post-index procedure. The EVOLVE II RCT was designed to test the hypothesis that the rate of 12-month TLF in patients treated with the SYNERGY Stent is non-inferior to the rate of 12 month TLF in patients treated with the PROMUS Element Plus Stent control.

In the EVOLVE II RCT, MI was defined as follows:

- Peri-procedural MI:
  i) Development of new pathological Q-waves or
  ii) Elevation of CK-MB levels >3x ULN, or if CKMB is not performed total CK must be >2x ULN, or if Troponin was only available enzyme, it must be >3x ULN. There must also be no evidence of pre-procedure biomarker elevations, or one of the following must be true: ≥50% increase in cardiac biomarker result, or evidence that cardiac biomarker values were decreasing prior to suspected MI or
  iii) Autopsy evidence of acute MI.
- Spontaneous MI definition: Detection of rise and/or fall of CK-MB or Troponin with at least one value above 99th percentile of ULN, together with evidence of myocardial ischemia and at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, development of new pathological Q-waves, imaging evidence of new loss of myocardium or new regional wall abnormality.

A total of 1,684 patients (846 SYNERGY Stent and 838 PROMUS Element Plus Stent) were randomized and enrolled at 125 sites in the Asia-Pacific region, Europe, Japan, Canada and the United States. 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.

Follow-up included clinical assessments at 30 days, 6, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12 month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study stent (SYNERGY Stent or PROMUS Element Plus Stent). The study is now complete including follow up through 5 years.

Results are presented in Tables 10.2.1 to 10.2.9.

Demographics: Patients were well-matched for baseline demographics. Average age was 63.48±10.44 and 63.92±10.50 in the SYNERGY and PROMUS Element Plus Stent groups, respectively. Approximately 70.6% of patients in the SYNERGY Stent group and 72.7% of patients in the PROMUS Element Plus Stent group were male, and 31.1% of patients in the SYNERGY group and 30.8% in the PROMUS Element Plus Stent group had medically treated diabetes. More than a third of patients in each treatment group had unstable angina and more than a quarter had MI diagnosed before the index procedure.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.62±0.49 mm and 2.63±0.50 mm for the SYNERGY and PROMUS Element Plus, respectively. Average lesion length was 14.09±7.50 mm and 13.67±7.00 mm for the SYNERGY and PROMUS Element Plus Stent groups, respectively. In both groups,

diameter stenosis was approximately 66%. More than 20% of patients in each treatment group had multiple lesions treated (≥2 lesion), and over 75% of treated lesions were type B2/C complex lesions.

[11] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

Table 10.2.1. EVOLVE II RCT 12 Month and 5-Year Clinical Results.

	12-Month (Intent-to-Treat population)		5-Year (Safety population)	
	SYNERGY (N=846*)	**PROMUS Element Plus[1] (N=838*)**	**SYNERGY (N=845*)**	**PROMUS Element Plus[1] (N=829*)**
EFFICACY				
TVR, Overall	3.8% (32/832)	3.6% (29/808)	11.9% (96/807)	11.1% (87/781)
TLR, Overall	2.6% (22/832)	1.7% (14/808)	6.7% (54/807)	5.2% (41/781)
TLR, PCI	2.0% (17/832)	1.7% (14/808)	6.1% (49/807)	4.9% (38/781)
TLR, CABG	0.6% (5/832)	0.0% (0/808)	1.0% (8/807)	0.4% (3/781)
Non-TLR, Overall	1.8% (15/832)	2.2% (18/808)	6.7% (54/807)	7.7% (60/781)
Non-TLR, PCI	1.4% (12/832)	1.9% (15/808)	6.2% (50/807)	6.8% (53/781)
Non-TLR, CABG	0.4% (3/832)	0.4% (3/808)	0.6% (5/807)	1.2% (9/781)
SAFETY				
Total Death	1.1% (9/832)	1.1% (9/808)	6.9% (56/807)	7.4% (58/781)
Cardiac Death or MI	5.6% (47/832)	5.6% (45/808)	12.5% (101/807)	12.3% (96/781)
Cardiac Death	0.5% (4/832)	0.9% (7/808)	3.5% (28/807)	4.2% (33/781)
MI	5.4% (45/832)	5.0% (40/808)	10.2% (82/807)	9.0% (70/781)
Q-wave MI	0.2% (2/832)	0.2% (2/808)	0.4% (3/807)	0.5% (4/781)
Non−Q-wave MI	5.2% (43/832)	4.7% (38/808)	9.9% (80/807)	8.5% (66/781)
ARC Stent Thrombosis**	0.6% (5/832)	0.7% (6/808)	2.5% (20/807)	3.2% (25/781)
Definite or Probable	0.4% (3/832)	0.6% (5/808)	0.7% (6/807)	0.9% (7/781)
Definite	0.2% (2/832)	0.2% (2/808)	0.6% (5/807)	0.5% (4/781)
Probable	0.1% (1/832)	0.4% (3/808)	0.1% (1/807)	0.4% (3/781)

[1] DES Control

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2-5 year clinical outcomes are based on the safety population only including patients who received a study stent.

Numbers are % (count/sample size).

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

** Includes the categories “possible”, “probable”, and “definite”.

Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Primary Endpoint (12 Month TLF): The primary endpoint was met. The SYNERGY Stent was shown to be non-inferior to the PROMUS Element Plus Stent with regard to the rate of 12 month TLF (Table 10.2.2).

Table 10.2.2 EVOLVE II RCT Primary Endpoint

Per Protocol Patients	SYNERGY (N=843)	PROMUS Element Plus[1] (N=829)	Difference	One-sided 97.5% Farrington-Manning Upper Confidence Bound	Non-Inferiority Margin	*P* value[2]
	6.4% (53/823)	6.4% (51/796)	0.0% [-2.4%, 2.4%]	2.51%	4.4%	0.0003
Intent-to-Treat Patients	**SYNERGY (N=846)**	**PROMUS Element Plus[1] N=838)**	**Difference**	**One-sided 97.5% Farrington-Manning Upper Confidence Bound**	**Non-Inferiority Margin**	***P* value[2]**
	6.7% (55/826)	6.5% (52/804)	0.2% [-2.2%, 2.6%]	2.68%	4.4%	0.0005

[1] DES Control
[2] *P* values are one-sided from the Farrington-Manning test and are based on the standard normal distribution.
12 Month TLF: the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 10.2.3 EVOLVE II Post-Procedure Angiographic Results by Lesion

Angiographic Outcomes	SYNERGY™ (N=1059 Lesions, N=846 Subjects)	PROMUS Element ™ Plus[1] (N=1043 Lesions, N=838 Subjects)
MLD (mm), In-stent	2.44 ± 0.44	2.46 ± 0.44
MLD (mm), Analysis Segment	2.10 ± 0.47	2.10 ± 0.47
Acute Gain (mm), In-stent	1.55 ± 0.45	1.57 ± 0.45
Acute Gain, Analysis Segment (mm)	1.22 ± 0.48	1.21 ± 0.47
% DS, In-stent	7.19 ± 9.16	6.55 ± 9.71
% DS, Analysis Segment	20.60 ± 8.41	20.93 ± 9.13

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

Table 10.2.4 EVOLVE II 5-Year ARC Definite and Probable Stent Thrombosis

Intent-to-Treat and Safety Patients[1]	SYNERGY (N=846* Subjects)	PROMUS Element Plus[4] (N=838* Subjects)
ARC Definite & Probable Stent Thrombosis[2]	0.7% (6/807)	0.9% (7/781)
Acute ST (≤24 hrs)	0.2% (2/846)	0.0% (0/838)
Subacute ST (>24 hrs and ≤30 days)	0.1% (1/846)	0.6% (5/834)
Late ST (>30 days and ≤12 months)[3]	0.0% (0/843)	0.0% (0/826)
Very Late ST (>365 days and ≤1855)	0.4% (3/826)	0.2% (2/802)

[1] 1-year outcomes are based on ITT. 1-5 and 2-5 year clinical outcomes are based on the Safety population only including patients who received a study stent.

[2] To be included in the calculation of 5-year stent thrombosis (ST) rate, a patient either had to have a CEC confirmed safety event during the 5 years or had to be CEC event-free during the 5 years with last follow-up on or after the 5-year visit window.

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

[4] DES Control

Academic Research Consortium (ARC) stent thrombosis is defined as follows.[12]

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

Numbers are % (Count/Sample Size).

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

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

[12] Cutlip DE, Windecker S, Mehran R, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation.2007;115:2344-2351.

10.2.5 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate 1.5 SE, All Patients (N=1684)

	Event Rate	Event Free	Log-Rank *P* value
SYNERGY	6.7%	93.3%	0.8314
PROMUS Element Plus	6.2%	93.8%	

Results in Males and Females

EVOLVE II was not designed or powered to study safety or effectiveness of the SYNERGY Stent versus the PROMUS Element Plus Stent in gender-specific subgroups, so these analyses are considered hypothesis-generating.

In the EVOLVE II ITT population, of the 846 patients randomized to SYNERGY, 597 patients were male (70.6%) and 249 patients were female (29.4%). The proportions in the PROMUS Element Plus group were similar (72.7% males, 27.3% females).

In the United States, an estimated 15,400,000 adults age 20 and older (7.9% of men and 5.1% of women) suffer from coronary artery disease (CAD).[13] However, it is estimated that only 33% of annual PCIs are performed in women. In PCI clinical trials, women represent only 25 – 35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology,[14,15] which may lead to under-diagnosis and under-referral of female patients with CAD. Once diagnosed and treated, poorer revascularization outcomes have been reported in women due to smaller coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men.

In patients treated with the SYNERGY Stent, the 12 month rate of TLF was 7.0% in males and 5.7% in females. In patients treated with the PROMUS Element Plus Stent, the 12 month rate of TLF was 5.6% in males and 8.7% in females (Table 10.2.6.). 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.

[13] Go AS, Mozaffarian D, Roger VL, et al. Executive Summary: Heart Disease and Stroke Statistics—2014 Update: A Report From the American Heart Association. Circulation. 2014;129(3):399-410

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

[15] Lundberg G, King S. Coronary Revascularization in Women. Clin Cardiol. 2012;35(3):156-159

Table 10.2.6 EVOLVE II RCT Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=1684)

12 month TLF	SYNERGY Stent (N=846)	PROMUS Element Plus Stent (N=838)	Difference
Female (N=478)	**(N=249)**	**(N=229)**	
	5.7% (14/244)	8.7% (19/218)	-3.0% [-7.7%, 1.8%]
Male (N=1206)	**(N=597)**	**(N=609)**	
	7.0% (41/582)	5.6% (33/586)	1.4% [-1.4%, 4.2%]
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (count/sample size). 12 Month TLF is the proportion of subjects who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion, MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.			

Table 10.2.7 shows EVOLVE II RCT 12 month and 5-Year clinical results for SYNERGY Stent male and female patients. Outcomes were similar in male and female patients.

Table 10.2.7 EVOLVE II 12 Month and 5-Year Clinical Endpoints by Gender SYNERGY Stent Male and Female Patients

	12-Month (ITT population)		5-Year (Safety population)	
	SYNERGY Stent Female Subjects (N=249*)	**SYNERGY Stent Male Subjects (N=597*)**	**SYNERGY Stent Female Subjects (N=249*)**	**SYNERGY Stent Male Subjects (N=596*)**
Efficacy				
TVR, Overall	3.3% (8/246)	4.1% (24/586)	11.6% (28/241)	12.0% (68/566)
TLR, Overall	2.4% (6/246)	2.7% (16/586)	7.1% (17/241)	6.5% (37/566)
TLR, PCI	2.0% (5/246)	2.0% (12/586)	6.2% (15/241)	6.0% (34/566)
TLR, CABG	0.4% (1/246)	0.7% (4/586)	1.2% (3/241)	0.9% (5/566)
Non-TLR, Overall	1.6% (4/246)	1.9% (11/586)	6.6% (16/241)	6.7% (38/566)
Non-TLR, PCI	1.6% (4/246)	1.4% (8/586)	6.2% (15/241)	6.2% (35/566)
Non-TLR, CABG	0.0% (0/246)	0.5% (3/586)	0.8% (2/241)	0.5% (3/566)
TLF	5.7% (14/246)	7.0% (41/586)	15.4% (37/241)	14.0% (79/566)
Safety				
Total Death	1.2% (3/246)	1.0% (6/586)	9.1% (22/241)	6.0% (34/566)
Cardiac Death or MI	5.3% (13/246)	5.8% (34/586)	14.1% (34/241)	11.8% (67/566)
Cardiac Death	0.8% (2/246)	0.3% (2/586)	3.3% (8/241)	3.5% (20/566)
MI	4.5% (11/246)	5.8% (34/586)	11.2% (27/241)	9.7% (55/566)
Q-wave MI	0.0% (0/246)	0.3% (2/586)	0.4% (1/241)	0.4% (2/566)
Non-Q-wave MI	4.5% (11/246)	5.5% (32/586)	10.8% (26/241)	9.5% (54/566)
ARC Stent Thrombosis	1.2% (3/246)	0.3% (2/586)	2.9% (7/241)	2.3% (13/566)
Definite or Probable	0.8% (2/246)	0.2% (1/586)	1.2% (3/241)	0.5% (3/566)
Definite	0.4% (1/246)	0.2% (1/586)	0.8% (2/241)	0.5% (3/566)
Probable	0.4% (1/246)	0.0% (0/586)	0.4% (1/241)	0.0% (0/566)

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2- 5 year clinical outcomes are based on the safety population only including patients who received a study stent.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (count/sample size).
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass grafting; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization.

Tables 10.2.8 and 10.2.9 show the cumulative rate of TLF through 12 months for males and females in both the SYNERGY and PROMUS Element Plus Stent, respectively. This post hoc analysis shows a difference in treatment and gender groups. 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.

Table 10.2.8 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Male Patients (N=1206)

	Event Rate	Event Free
SYNERGY™ (N=597)	7.0%	93.0%
PROMUS Element™ Plus (N=609)	5.5%	94.5%

Table 10.2.9 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Female Patients (N=478)

	Event Rate	Event Free
SYNERGY (N=249)	6.0%	94.0%
PROMUS Element Plus (N=229)	8.4%	91.6%

10.3 EVOLVE II Diabetic (DM) Sub-study

Primary Objective: The primary objective of the EVOLVE II DM sub-study was to evaluate the safety and effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment diabetic patients with atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Eligible patients were to have diabetes (treated with oral agent, insulin or another injectable agent), be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[16] Patients could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was the rate of target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion
(TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death, at 12 months post-index procedure. The EVOLVE II DM sub-study was designed to test the hypothesis that the rate of 12-month TLF in patients treated with the SYNERGY Stent was less than a prespecified performance goal (PG) of 14.5%. The PG was based on data from patients with diabetes in the PLATINUM,
SPIRIT IV, COMPARE, and EVOLVE trials adjusted for the expected increase in the 12-month non-Q-wave MI rate using CK-MB >3x upper limit of normal (ULN) instead of the historical definition with total CK >2x ULN.

The EVOLVE II DM Sub-study pooled: 1) diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patient with 2) diabetes subjects enrolled in the non-randomized Diabetes single-arm study (203 patients from 48 sites in Asia-Pacific region, Europe, Canada and the United States), following completion of EVOLVE II RCT enrollment. A total of 460 intention-to-treat patients were evaluable for the 12 month primary endpoint.

Follow-up included clinical assessments at 30 days, 6, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12 month follow-up, the study population was reduced to a prespecified cohort (Safety Population), which consists of all patients who received a study stent.

The study is now complete including follow up through 5 years.

Results are presented in Tables 10.3.1 and 10.3.2. The primary endpoint of the DM Sub-study was met as the one-sided upper 97.5% confidence bound for 1 year TLF was below the pre-specified performance goal of 14.5% (Table 10.3.2). A poolability analysis found that the TLF rate in diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patients) was higher than the TLF rate in the diabetic patients enrolled in the non-randomized Diabetes single-arm study (203 subjects) due to differences in the geographic pattern of enrollment and in biomarker collection between the two cohorts. The differences in the 1 year TLF rate were driven primarily by non-Q-wave MI and particularly peri-procedural non-Q-wave MI. When non-Q-wave MI or peri-procedural non-Q-wave MI were excluded from the calculation of TLF, the TLF rate was not statistically different between the two cohorts (Table 10.3.3). Sensitivity analysis showed that the primary endpoint would still have been met even if the TLF rate in the single arm cohort was not lower than in the diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT.

Demographics: Average age of patients in the DM sub-study was 65% and 70% of the patients were male. The majority of the patients were treated with an oral agent (83.3%, 388/466)) while 37.3% (174/466) of patients were treated with insulin and 0.6% (0/466) were treated with an injectable agent other than insulin. More than a third of patients had unstable angina and more than a quarter had MI diagnosed before the index procedure.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.56±0.50 and average lesion length was 14.10±7.49. Baseline diameter stenosis was 65.47±11.70. Twenty percent of patients had 2 lesions treated and 74.9% of treated lesions were type B2/C complex lesions.

[16] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

Table 10.3.1 EVOLVE II DM Sub-study 12 Month and 5 -Year Clinical Results

	12-Month (ITT population)	**5-Year (Safety population)**
	SYNERGY (N=466*)	**SYNERGY (N=463*)**
EFFICACY		
TVR, Overall	5.3% (24/455)	14.8% (66/446)
TLR, Overall	4.4% (20/455)	9.0% (40/446)
TLR, PCI	3.5% (16/455)	8.1% (36/446)
TLR, CABG	0.9% (4/455)	1.6% (7/446)
Non-TLR, Overall	1.8% (8/455)	9.0% (40/446)
Non-TLR, PCI	1.3% (6/455)	8.3% (37/446)
Non-TLR, CABG	0.4% (2/455)	1.1% (5/446)
SAFETY		
Total Death	1.3% (6/455)	10.3% (46/446)
Cardiac Death or MI	6.2% (28/455)	14.1% (63/446)
Cardiac Death	0.7% (3/455)	4.3% (19/446)
MI	5.9% (27/455)	11.2% (50/446)
Q-wave MI	0.4% (2/455)	0.7% (3/446)
Non−Q-wave MI	5.5% (25/455)	10.8% (48/446)
ARC Stent Thrombosis**	1.5% (7/455)	3.1% (14/446)
Definite or Probable	1.1% (5/455)	1.1% (5/446)

Definite	1.1% (5/455)	1.1% (5/446)
Probable	0.0% (0/455)	0.0% (0/446)

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2-5 year clinical outcomes are based on the safety population only including patients who received a study stent.
Numbers are % (count/sample size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
** Includes the categories "possible", "probable", and "definite".
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 10.3.2 EVOLVE II DM Sub-study Primary Endpoint

Primary Endpoint: 12 month TLF	**Overall Diabetic Subjects**	**One-sided Clopper-Pearson 97.5% Upper Confidence Bound**	**Performance Goal**	**One Sided *P* value[1]**
Intent-to-Treat Subjects	**(N=466)** 7.5% (34/451)	10.4%	14.5%	<0.0001
Per Protocol Subjects	**(N=463)** 7.4% (33/448)	10.2%	14.5%	<0.0001

Numbers are % (counts/sample size)
[1] One-group Clopper-Pearson test
Abbreviations: 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)

Table 10.3.3 EVOLVE II DM Sub-study TLF with and without Peri-procedure NQWMI

Event	**Diabetic Subjects from RCT (N=263 Subjects)**	**Subjects from Diabetic Substudy (N=203 Subjects)**	***P* value**
TLF	10.2% (26/256)	4.0% (8/199)	0.0135
TLF excluding non-Q-wave MI	6.6% (17/256)	3.0% (6/199)	0.0799
TLF excluding Peri-Procedure non-Q-wave MI	6.6% (17/256)	3.5% (7/199)	0.1393

10.4 EVOLVE II Quantitative Coronary Angiography (QCA) Trial

Primary Objective: The primary objective of the EVOLVE II QCA Trial was to evaluate the clinical, angiographic, and IVUS outcomes of the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of ≥2.25 mm to ≤4.00 mm in diameter (by visual estimate).

Design: EVOLVE II QCA is a prospective, single-arm, multi-center, observational trial with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[17] Patients could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was in-stent late loss at 9 months post-procedure as measured by quantitative coronary angiography (QCA). No formal statistical testing was performed for the primary endpoint in this single arm observational trial. All patients were required to undergo 9 month angiography and IVUS assessments.

For The 9 month in-stent late loss, the performance goal was based on historical PLATINUM QCA and PROMUS™ arm of RESOLUTE all-comers results.

No adjustments were made for multiple comparisons. MI was defined as described in the EVOLVE II (see section 10.2).

A total of 100 patients were enrolled at 12 sites. Of the 100 patients included in the intent-to-treat analysis set, all were evaluable for the 9 month primary endpoint, 95 underwent angiography at 9 months post procedure, and 90 underwent IVUS at 9 months post procedure.

Follow-up included clinical assessments at 30 days, 9 months and 12 months post index procedure, and angiographic and IVUS assessments at 9 months post procedure. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment). The study is now complete.

Results are presented in Tables 10.4.1 to 10.4.4.

Demographics: Average age was 64.49 ± 10.21. 80% of patients were male, and 17% of patients had medically treated diabetes.

Baseline lesion characteristics: Reference vessel diameter was 2.66 ± 0.46 mm with baseline lesion length 14.38 ± 7.49 mm. Percent diameter stenosis was 67.54±9.59 and 74.1% of treated lesions were type B2/C.

[17] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

Table 10.4.1 EVOLVE II QCA 9 Month Clinical Results, Intent-to-Treat, All Patients

	SYNERGY Stent (N=100)
EFFICACY	
TVR, Overall	3.0% (3/100)
TLR, Overall	1.0% (1/100)
TLR, PCI	1.0% (1/100)
TLR, CABG	0.0% (0/100)
Non-TLR, Overall	2.0% (2/100)
Non-TLR, PCI	2.0% (2/100)
Non-TLR, CABG	0.0% (0/100)
SAFETY	
Total Death	0.0% (0/100)
Cardiac Death or MI	5.0% (5/100)
Cardiac Death	0.0% (0/100)
MI	5.0% (5/100)
Q-wave MI	0.0% (0/100)
Non−Q-wave MI	5.0% (5/100)
ARC Stent Thrombosis	0.0% (0/100)
Definite or Probable	0.0% (0/100)
Definite	0.0% (0/100)
Probable	0.0% (0/100)

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

Primary Endpoint (9 month In-stent Late Loss by QCA): In-stent late loss of 0.23±0.34 mm was significantly less than the performance goal of 0.40 mm (P<0.0001) at 9 months. No adjustments to *P* values were made for multiple comparisons.

Table 10.4.2 EVOLVE II QCA Primary Endpoint: 9 Month In-stent Late Loss

Per-protocol and Intent to treat	**SYNERGY Stent (N=100)**	**[95% CI]**	**One-sided 95% upper confidence bound**	**Performance Goal**	***P* value[1]**
9 Month In-Stent Late Loss, mm	0.23±0.34	[0.16, 0.29]	0.30	0.40	<.0001
[1] A one-group t-test is used.					

Table 10.4.3 EVOLVE II QCA Angiographic and IVUS Results

Angiographic Outcomes[1]	**SYNERGY (N=100)**
MLD (mm), In-stent	
Post-Procedure	2.51±0.44
9 Month	2.29±0.46
MLD (mm), Analysis Segment	
Post-Procedure	2.16±0.45
9 Month	2.06±0.46
Acute Gain (mm), In-stent	1.65±0.41
Acute Gain, Analysis Segment (mm)	1.30±0.43
% DS, In-stent	
Post-Procedure	6.83±8.57
9 Month	13.54±12.49
% DS, Analysis Segment	
Post-Procedure	20.02±7.77
9 Month	22.39±11.27
Late Loss, In-stent (mm) (9 months)	0.22±0.33
Late Loss, Analysis Segment (mm) (9 months)	0.10±0.30
Binary Restenosis	
In-stent Restenosis	1.8% (2/110)
Analysis segment restenosis	3.6% (4/110)
IVUS Outcomes	
Neointimal Volume (mm^3) (9 months)	9.67±14.57
% In-stent Net Volume Obstruction (9 months)	5.19±5.67
Incomplete Apposition	
Late (9 months)	6.5% (6/92)

Late Acquired	3.4% (3/88)
[1] Includes all patients with paired lesion data Numbers are % (count/sample size) or mean±SD (n).	

Results in Males and Females:

EVOLVE II QCA was not designed or powered to study safety or effectiveness of the SYNERGY Stent in gender-specific subgroups, so these analyses were performed *post hoc* and are considered hypothesis-generating.

In the EVOLVE II QCA ITT population, of the 100 patients enrolled, 80 patients were male (80.0%) and 20 patients were female (20.0%). In patients treated with the SYNERGY Stent, the 9-month rate of TLF was 5% in males and 10% in females (Table 10.3.4). Table 10.3.4 also shows the EVOLVE II QCA primary endpoint for males and females. Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 10.4.4 EVOLVE II QCA 9 Month Results by Gender, Intent-to-Treat, SYNERGY Male and Female Patients (N=100)

	SYNERGY Stent Male Patients (N=80)	**SYNERGY Stent Female Patients (N=20)**
9 Month TLF	5.0% (4/80)	10.0% (2/20)
9 Month In-stent Late Loss	0.22±0.34	0.26±0.33
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (count/sample size). TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 270 days post-procedure out of the population that have been followed for at least 24 days or who have experienced a TLF up to 270 days post-procedure.		

10.5 EVOLVE Short DAPT Study

Primary Objective: The primary objective of the EVOLVE Short DAPT Study is to assess the safety of 3-month DAPT in subjects at high risk for bleeding undergoing PCI with the SYNERGY Stent System.

Design: The EVOLVE Short DAPT Study* is a prospective, multi-center, single-arm study in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent. A historical control and a propensity score approach was used to assess the safety of 3-month DAPT in high bleeding risk patients. High bleeding risk subjects were enrolled if they met one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL. Subjects were prescribed dual antiplatelet therapy ($P2Y_{12}$ inhibitor + aspirin) between 0-3 months post-procedure. Aspirin was optional between 0-3 months for subjects on chronic anticoagulation. Subjects were eligible to discontinue $P2Y_{12}$ inhibitor at 3 months if they were compliant with the prescribed dual antiplatelet therapy and were free from events between 0-3 months (stent thrombosis, myocardial infarction, revascularization, or stroke). Subjects that discontinued $P2Y_{12}$ inhibitor at 3-months were prescribed aspirin through the end of study. The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or MI, and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis related to SYNERGY. The control group for the death/MI primary endpoint includes propensity-matched historical sirolimus, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the PROMUS Element Plus Post-Approval Study (PE+PAS), PE-PROVE Study and the DAPT Study. The second co-primary endpoint was ARC definite/probable stent thrombosis related to SYNERGY compared to pre-specified performance goal (1.0%). The pre-specified secondary endpoint is the rate of bleeding, using the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) between 3-15 months post-index procedure in subjects not receiving chronic anticoagulation. The control group for the secondary bleeding endpoint includes propensity-matched historical sirolimus-, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the DAPT Study, excluding subjects on chronic anticoagulation. A total of 2,009 patients were enrolled at 110 sites in the United States, Europe, Brazil and Japan, of which 1,487 patients were eligible to and discontinued $P2Y_{12}$ inhibitor at 3-months (3-month DAPT group). Patients were followed at 3-, 6-, 12- and 15-months post-index procedure. The study is considered complete with follow-up through 15-months.

Results are presented in Tables 10.5.1 to 10.5.6.

Demographics: In subjects that discontinued $P2Y_{12}$ inhibitor at 3-months (n=1,487), the mean age in the 3-month group was 75.7 years, 34.0% were female, and subjects had a mean BMI of 28.7.

Baseline/Lesion Characteristics: Thirty-six percent subjects that discontinued $P2Y_{12}$ inhibitor at 3-months had diabetes, 26% had unstable angina, 48% stable angina and 9% silent ischemia (STEMI and NSTEMI patients were excluded from enrollment). Prior myocardial infarction, heart failure and atrial fibrillation were present in 23%, 26% and 31% of subjects, respectively. Visually-estimated mean reference vessel diameter was 3.0±0.5 mm, mean lesion length was 17.2±9.5 mm, and mean percent diameter stenosis was 82.6±9.8%.

Table 10.5.1. EVOLVE Short DAPT Study 3-15 months Outcomes in the 3-Month DAPT group

	SYNERGY (N=1487)
TVR, Overall	2.6% (38/1457)
TLR	1.9% (28/1457)
Non-TLR	1.2% (17/1457)
Total Death	4.3% (62/1457)
Death or MI	5.8% (84/1457)
Cardiac Death or MI	3.6% (52/1457)
Cardiac Death	2.1% (30/1457)
Non-Cardiac Death	1.9% (27/1457)
MI	1.9% (27/1457)
Q-wave MI	0.2% (3/1457)
Non−Q-wave MI	1.7% (25/1457)
Stroke	1.4% (21/1457)
BARC 2,3,5 Bleeding	7.1% (103/1457)
BARC 2	4.6% (67/1457)
BARC 3	2.7% (40/1457)
BARC 5	0.2% (3/1457)
ARC Stent Thrombosis; Definite or Probable; Related to SYNERGY	0.2% (3/1457)

Co-Primary Endpoints: The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or myocardial infarction (MI), and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST), related to the SYNERGY stent. The EVOLVE Short DAPT study was considered a success as both the co-primary endpoints of death/MI and ARC definite/probable ST were met. In high bleeding risk patients, death/MI in the 3-month DAPT group implanted with the SYNERGY stent was non-inferior to 12-month DAPT historical control. ARC definite/probable ST related to the SYNERGY stent in the 3-month DAPT group treated with the SYNERGY stent was significantly lower than the pre-specified performance goal. Results for the two co-primary endpoints are in Tables 10.5.2 and 10.5.3.

Table 10.5.2: Co-Primary Endpoint: Death/MI between 3-15 months

12-month DAPT[d] N=1948	3-month DAPT N=1487	Difference [95% CI]	One-sided 97.5% UCB[a]	NI Margin	P-value[c]
5.70%	5.58%	-0.12% [-1.87%, 1.63%]	1.63%	2.52%	0.0016

Numbers are % (count/sample size)
a: Z-test upper confidence bound (UCB)
b: Non-inferiority margin
c: *P* value is from one-tailed Z-test and is based on normal approximation to binomial
Subjects with respective event or sufficient follow up were included in the denominator; N=1454 in 3-month DAPT test group and N=1493 in 12-month DAPT control group
d: The control group for the death/MI primary endpoint includes propensity-matched historical sirolimus, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the PROMUS Element Plus Post-Approval Study (PE+PAS), PE-PROVE Study and the DAPT Study.

Table 10.5.3 Co-Primary Endpoint (3-15-month ARC Definite/Probable Stent Thrombosis Related to SYNERGY)

3-month DAPT (N=1487)	[95% CI]	One-sided 97.5% UCB[a]	Performance goal	P-value[b]
0.2% (3/1396)	[0.04%, 0.63%]	0.63%	1.0%	0.0005

Numbers are % (count/sample size)
a: Exact test upper confidence bound (UCB)
b: *P* value is from one-sided exact test for single proportion
Subjects with respective event or sufficient follow up were included in the denominator; N=1397 in 3-month DAPT test group

Secondary Endpoint: The secondary endpoint is the rate of bleeding, using the BARC classification (types 2, 3 and 5) between 3- and 15-months post index procedure in subjects not receiving chronic anticoagulation. The study secondary endpoint was not met; however, residual confounding despite propensity matching and better ascertainment of bleeding events in the EVOLVE Short DAPT Study as compared to the historical control may have contributed to this outcome as shorter duration DAPT is expected to reduce the risk of bleeding. Results for the secondary endpoint are in Table 10.5.4.

Table 10.5.4: Secondary Endpoint: BARC 2/3/5 Bleeding between 3-15 months

12-month DAPT N=1333	3-month DAPT N=1032	Difference [95% CI]	One-sided 97.5% UCB[a]	Superiority Test P-value[b]
4.17%	6.26%	2.10% [-0.10%, 4.29%]	4.29%	0.9820

Numbers are % (count/sample size)
a: Z-test upper confidence bound (UCB)
b: *P* value is from one-tailed Z-test and is based on normal approximation to binomial
Subjects with respective event or sufficient follow up were included in the denominator; N=974 in 3-month DAPT test group and N=947 in 12-month DAPT control group

Results in Males and Females

The EVOLVE Short DAPT Study was not powered to evaluate safety or effectiveness of the SYNERGY Stent in gender-specific subgroups, therefore these analyses are considered hypothesis-generating.

In the EVOLVE Short DAPT Study, of the 1,487 subjects that discontinued P2Y12 inhibitor at 3-months (3-Month DAPT group), 981 patients were male (66%) and 506 patients were female (34%).

In the 3-month DAPT group, the death/MI rate between 3-15 months was 6.1% in males and 5.1% in females. The ARC definite/probable stent thrombosis (related to SYNERGY) rate was 0.3% in males and 0.0% in females. The BARC 2,3,5 bleeding rate was 5.9% in males and 6.0% in females. No statistically significant differences between male and females were observed for the pre-specified primary and secondary endpoints. The overall

conclusions of the trial regarding the safety of the SYNERGY Stent with 3-months of DAPT in patients at high risk of bleeding can be generalized to males and females.

Table 10.5.5 EVOLVE Short DAPT Study – Co-Primary and Secondary Endpoints (3-15 months) in the 3-Month DAPT group (n=1487)

	3-Month DAPT Group (N=1487)	
	Male (N=981)	**Female (N=506)**
Death and MI	6.1% (59/966)	5.1% (25/491)
ARC ST (Definite/Probable) related to SYNERGY stent	0.3% (3/966)	0.0% (0/491)
Bleeding (BARC 2/3/5)	5.9% (37/624)	6.0% (23/386)

Table 10.5.6. shows EVOLVE Short DAPT Study clinical results for the 3-Month DAPT group between 3-15 months for male and female patients. Outcomes were similar in male and female patients although the trend suggests fewer ischemic complications in females.

Table 10.5.6 EVOLVE Short DAPT Study Clinical Outcomes by Gender; 3-Month DAPT group (3-15 months)

	3-Month DAPT Group (n=1487)	
	SYNERGY Stent Male Subjects (N=981)	**SYNERGY Stent Female Subjects (N=506)**
TVR, Overall	2.9% (28/966)	2.0% (10/491)
TLR	2.1% (20/966)	1.6% (8/491)
Non-TLR	1.1% (11/966)	1.2% (6/491)
TLF	4.7% (45/966)	3.9% (19/491)
Total Death	4.3% (42/966)	4.1% (20/491)
Death or MI	6.1% (59/966)	5.1% (25/491)
Cardiac Death or MI	3.8% (37/966)	3.1% (15/491)
Cardiac Death	2.1% (20/966)	2.0% (10/491)
Non-Cardiac Death	1.9% (18/966)	1.8% (9/491)
MI	2.0% (19/966)	1.6% (8/491)
Q-wave MI	0.2% (2/966)	0.2% (1/491)
Non-Q-wave MI	1.9% (18/966)	1.4% (7/491)
Stroke	1.2% (12/966)	1.8% (9/491)
BARC 2,3,5 Bleeding	7.0% (68/966)	7.1% (35/491)
BARC 2	5.0% (48/966)	3.9% (19/491)
BARC 3	2.5% (24/966)	3.3% (16/491)
BARC 5	0.1% (1/966)	0.4% (2/491)
ARC Stent Thrombosis	1.2% (12/966)	0.6% (3/491)
Definite or Probable	0.3% (3/966)	0.0% (0/491)
Definite	0.3% (3/966)	0.0% (0/491)
Probable	0.0% (0/966)	0.0% (0/491)

The overall conclusions of the trial regarding the safety of the SYNERGY Stent with 3-months of DAPT in patients at high risk of bleeding can be generalized to males and females.

11 INDIVIDUALIZATION OF TREATMENT:

See Section 6.7, Use in Special Populations and Section 6.8, Lesion/Vessel Characteristics.

The risks and benefits should be carefully considered for each patient before use of the SYNERGY™ Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged antiplatelet therapy. On the basis of randomized clinical trial protocols and current clinical practice guidelines, a $P2Y_{12}$ inhibitor should be given for at least 6 months after everolimus-eluting stent (EES) implantation and ideally up to 12 months. Aspirin should be administered concomitantly with the $P2Y_{12}$ inhibitor and then continued indefinitely. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease) in whom antiplatelet therapy would be contraindicated.

Premorbid conditions that increase the risk of poor initial results or the risks of referral for emergency bypass surgery (diabetes mellitus, renal failure and severe obesity) should be reviewed.

12 PATIENT COUNSELING INFORMATION:

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks/benefits issues for this particular patient.
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide (included in the package and available on-line) which includes both product information and a stent implant card.
- An Angioplasty and Stent Education Guide (available on-line or by request) which includes information on coronary artery disease, the implant procedure and frequently asked questions.

13 HOW SUPPLIED:

STERILE: This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize.

The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System is sterile, non-pyrogenic in unopened, undamaged packaging.
Do not use if package is opened or damaged.

Do not use if labeling is incomplete or illegible.

HANDLING and STORAGE: Keep dry and protect from light. Recommended storage at 25°C (77°F); excursions permitted to 15 °C – 30°C (59°F – 86°F).

Store product in outer carton.

DO NOT REMOVE FROM FOIL POUCH UNTIL READY FOR USE.

THE FOIL POUCH IS NOT A STERILE BARRIER.

Do not store devices where they are directly exposed to organic solvents or ionizing radiation.

The foil pouch contains nitrogen gas (N_2) and desiccant as a storage medium.

DISPOSAL INSTRUCTIONS: After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

14 OPERATIONAL INSTRUCTIONS:

14.1 Inspection Prior to Use

Check foil pouch for ‘‘Use By’’ date. Do not use the product after the ‘‘Use By’’ date. Carefully inspect the foil pouch and the sterile package before opening. If the integrity of the foil pouch or the sterile package has been compromised prior to the product ‘‘Use By’’ date (e.g., damage of the package), contact your local Boston Scientific representative for return information. Do not use if any defects are noted.

Note: At any time during use of the Monorail™ Stent Delivery System, if the proximal shaft (hypotube) has been bent or kinked, do not continue to use the catheter.

14.2 Materials Required (not included in Stent Delivery System package)

Quantity	Material
1	Appropriate guide catheter (see Table 2.1, SYNERGY Stent System Product Description)
2 – 3	20 ml (cc) syringe
1000 u/500 cc	Normal heparinized sterile saline
1	≤0.014 in (0.36 mm) guidewire
1	Hemostatic valve
1	Diluted contrast medium 1:1 with normal heparinized sterile saline
1	Inflation Device
1	Torque Device
1	Pre-deployment dilation catheter
1	Three-way stopcock
1	Appropriate arterial sheath

14.3 Preparation

14.3.1 Packaging Removal

Step **Action**

1. Open the outer box to reveal the foil pouch and carefully inspect the foil pouch for damage.
2. Carefully open the foil pouch by tearing along the tear strip as indicated on the foil pouch to access the sterile barrier package containing the stent delivery system.
3. Carefully inspect the sterile barrier package for damage.
4. Carefully peel open the sterile barrier using aseptic techniques and extract the stent delivery system.
5. Carefully remove the stent delivery system from its protective tubing for preparation of the delivery system. When using a Monorail™ system, do not bend or kink proximal shaft during removal.
6. Remove the product mandrel and stent protector by grasping the catheter just proximal to the stent protector, and with the other hand, grasp the distal end of the stent protector and gently remove.

Note: If unusual resistance is felt during product mandrel and stent protector removal, do not use the product and replace with another.

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7. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.

14.3.2 Guidewire Lumen Flush

Step **Action**

1. (Over-The-Wire only) Flush the stent delivery system guidewire lumen with normal heparinized saline through the straight arm of the Y connector manifold.
2. (Monorail system only) Flush the stent delivery system guidewire lumen with normal heparinized saline using the flushing needle supplied for the Monorail delivery system at the distal end.
3. Verify that the stent is positioned between the proximal and distal balloon markers. Check for bends, kinks and other damage. Do not use if any defects are noted.

Note: Avoid manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.

Note: Use caution while flushing guidewire lumen with flushing needle to avoid damage to catheter tip.

14.3.3 Balloon Preparation

Step	Action
1.	Stent contact with any fluid is not recommended, as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).
2.	Prepare inflation device/syringe with diluted contrast medium.
3.	Attach inflation device/syringe to stopcock; attach to inflation port. Do not bend the proximal shaft when connecting to inflation device/syringe.
4.	With tip down, orient stent delivery system vertically.
5.	Open stopcock to stent delivery system; pull negative for 15 seconds; release to neutral for contrast fill.
6.	Close stopcock to stent delivery system; purge inflation device/ syringe of all air.
7.	Repeat steps 4 through 6 until all air is expelled. If bubbles persist, do not use product.
8.	If a syringe was used, attach a prepared inflation device to stopcock.
9.	Open stopcock to stent delivery system.
10.	Leave on neutral.

14.3.4 Delivery Procedure

Step	Action
1.	Obtain vascular access according to standard PTCA practice. Select a guide catheter that provides adequate support and coaxial alignment with the coronary ostium to deliver interventional equipment.
2.	Pre-dilate the lesion/vessel with appropriate diameter balloon.
3.	Maintain neutral pressure on inflation device attached to stent delivery system.
4.	Backload stent delivery system onto proximal portion of guidewire while maintaining guidewire position across target lesion.
5.	Fully open hemostatic valve to allow for easy passage of the stent and prevent damage to the stent.
6.	Carefully advance the stent delivery system into the hub of the guide catheter. When using a Monorail stent delivery system be sure to keep the proximal shaft straight. Ensure guide catheter stability before advancing the stent delivery system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guide catheter, do not force passage. Resistance may indicate a problem, and use of excessive force may result in stent damage or stent dislodgment from the balloon. Maintain guidewire placement across the lesion, and remove the stent delivery system and guide catheter as a single unit.

7.	Advance the stent delivery system over the guidewire to target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque balloon markers as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also Precautions – Section 6.15, Stent Delivery System Removal). The inside edges of the marker bands indicate both the stent edges and balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

Note: If unusual resistance is felt at any time during lesion access before stent implantation, the stent delivery system and the guide catheter should be removed as a single unit. (See also Precautions – Section 6.15, Stent Delivery System Removal). Once the stent delivery system has been removed do not re-use.

8.	Sufficiently tighten the hemostatic valve. The stent is now ready to be deployed.

14.3.5 Deployment Procedure

Step	Action
1.	Inflate the delivery system expanding the stent to a minimum pressure of 11 atm (1117 kPa). Higher pressure may be necessary to optimize stent apposition to the arterial wall. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter of about 1.1 times the reference vessel diameter (see Table 14.1). Balloon pressure must not exceed rated burst pressure of 18 atm (1827 kPa) for the 2.25 mm – 2.75 mm diameter stents and 16 atm (1620 kPa) for the 3.00 mm – 5.00 mm diameter stent sizes (see Table 14.1).

2. Maintain inflation pressure for 15 – 30 seconds for full expansion of the stent.
3. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
4. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
5. If stent sizing/apposition requires optimization, re-advance the stent delivery system balloon, or another high-pressure, balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.
6. Inflate the balloon to the desired pressure while observing under fluoroscopy (refer to product labeling and/or Table 14.1 for balloon compliance chart). Deflate the balloon. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
7. If more than one SYNERGY™ Stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second SYNERGY Stent should be positioned inside of the deployed stent prior to expansion.
8. Reconfirm stent position and angiographic result. Repeat inflations until optimal stent deployment is achieved.

14.3.6 Removal Procedure

Step Action

1. Ensure balloon is fully deflated before delivery system withdrawal. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
2. Fully open rotating hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system.
4. Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

Post-Deployment Dilation of Stented Segments

Precaution: Do not dilate the stent beyond the limits tabulated below.

Nominal Stent Diameter (ID)	Dilation Limits (ID)*
2.25 mm, 2.50 mm, 2.75 mm	3.50 mm
3.00 mm, 3.50 mm	4.25 mm
4.00 mm, 4.50 mm, 5.00 mm	5.75 mm

*Max Stent Inner Diameter

All efforts should be taken to assure that the stent is not under-dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger post dilation balloon catheter may be used to expand the stent. The stent may be expanded using a low profile and

high pressure balloon catheter. If this is required, the stented segment should be re-crossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

Note: In line with Section 6.16, Post-Procedure: Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.

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5. Complete angiographic confirmation, remove devices, and close vascular access site according to standard practice.

14.4 In Vitro Information

Table 14.1 Typical SYNERGY Stent System Compliance

Pressure atm - (kPa)	Stent Inner Diameters (mm)							
	2.25 mm	2.50 mm	2.75 mm	3.00 mm	3.50 mm	4.00 mm	4.50 mm	5.00 mm
6 (607)						3.55		
7 (710)				2.72	3.19	3.68		
8 (814)	2.09			2.81	3.31	3.80	4.11	4.62
9 (910)	2.14	2.40	2.63	2.89	3.40	3.90	4.24	4.73
10 (1014)	2.19	2.46	2.70	2.96	3.47	3.98	4.35	4.85
11 Nominal (1117)	2.25	2.52	2.76	3.02	3.55	4.05	4.46	4.95
12 (1213)	2.29	2.57	2.82	3.06	3.60	4.11	4.54	5.03
13 (1317)	2.32	2.61	2.87	3.11	3.66	4.18	4.61	5.11
14 (1420)	2.36	2.65	2.90	3.15	3.70	4.22	4.68	5.17
15 (1517)	2.38	2.68	2.94	3.18	3.74	4.26	4.73	5.22
16*(1620)	2.41	2.71	2.97	3.21	3.78	4.31	4.78	5.28
17 (1724)	2.43	2.74	3.00	3.25	3.82	4.36	4.83	5.34
18* (1827)	2.46	2.77	3.03	3.29	3.88	4.43	4.89	5.39
19 (1924)	2.48	2.80	3.06	3.34	3.94	4.51	4.96	5.45
20 (2027)		2.83	3.10	3.39	4.01		5.04	5.50

* RATED BURST PRESSURE. DO NOT EXCEED.
Note: The Stent I.D. values listed are actual average stent inner diameters at the specific balloon inflation pressures obtained during in vitro testing at 37°C. Balloon pressure must not exceed rated burst pressure of 18 atm (1827 kPa) for the 2.25 mm – 2.75 mm diameter stents and 16 atm (1620 kPa) for the 3.00 mm – 5.00 mm diameter stent sizes.

15 WARRANTY STATEMENT:

Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from

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50815660-01

SYNERGY™ XD

MONORAIL™

Everolimus-Eluting Platinum Chromium Coronary Stent System

℞ ONLY

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

This device is supplied in sterile condition. All materials inside the sterile barrier pouch (the delivery system and stent, as well as the carrier tube and pouch liner) are sterile. The external surface of the sterile barrier pouch, as well as the product carton, should not be considered sterile.

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1 WARNING

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Boston Scientific representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

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2 DEVICE DESCRIPTION

The SYNERGY XD Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY XD Stent System) is a device/drug combination product consisting of a drug/polymer-coated balloon expandable stent, pre-mounted on a Monorail (MR) delivery catheter. The stent is made from a platinum chromium alloy (PtCr), which consists of platinum, chromium, iron, nickel, and molybdenum. The characteristics of the SYNERGY XD Stent System are described in Table 2.1. SYNERGY XD Stent System Product Description:

Table 2.1 SYNERGY™ XD Stent System Product Description

	SYNERGY XD Monorail™ Stent Delivery System
Drug Coated Stent	
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32, 38, 48*
Available Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50** and 5.00**
Stent Material	Platinum Chromium Alloy (PtCr) (PtCr alloy components: platinum, chromium, iron, nickel, and molybdenum)
Stent Strut Thickness	2.25 mm - 2.75 mm: 0.0029 inches (0.074 mm) 3.00 mm - 3.50 mm: 0.0031 inches (0.079 mm) 4.00 mm - 5.00 mm: 0.0032 inches (0.081 mm)
Drug Product	An abluminal (outer surface of the stent in contact with the vessel wall) coating of a bioabsorbable polymer carrier PLGA [poly (DL-lactide-co-glycolide)] with approximately 1 µg of everolimus per mm^2 of total stent surface area with a maximum nominal drug content of 364 µg on the largest stent.
Delivery System	
Effective Length	144 cm
Delivery System Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 23 cm from tip. 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: 11 atm (1117 kPA) Rated Burst Inflation Pressure: •Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) Diameters 3.00 mm – 5.00 mm: 16 atm (1620 kPa)
Catheter Shaft Outer Diameter	Proximal: 2.0F (0.67 mm) Distal: 2.25 mm – 2.75 mm: 2.6F (0.89 mm) 3.00 mm: •8 mm – 28 mm: 2.6F (0.89 mm) •32 mm – 48 mm: 2.7F 0.92 mm) 3.50 mm: •8 mm – 20 mm: 2.6F 0.89 mm) •24 mm – 48 mm: 2.7F (0.92 mm) 4.00 mm - 5.00 mm: 2.7F (0.92 mm)
Guide Catheter Minimum Inner Diameter Requirement	2.25 mm - 4.00 mm: ≥5F (0.056 inches/1.42 mm) 4.50 mm - 5.00 mm: ≥6F (0.070 inches/1.78 mm)

* The 48 mm length is not available in 2.25 mm, 4.50 mm or 5.00 mm diameters.
** The 4.50 mm and 5.00 mm diameter is not available in 8 mm, 38 mm and 48 mm lengths.

2.1 User Information

Only Physicians who have received adequate training should perform implantation of the stent.

2.2 Non-Pyrogenic

SYNERGY XD Everolimus-Eluting Platinum Chromium Coronary Stent System is sterile, non-pyrogenic in unopened, undamaged packaging.

2.3 Device Component Description

The SYNERGY XD Stent System consists of a platinum chromium stent platform with an abluminal drug/polymer coating mounted onto Monorail Delivery System.

The SYNERGY XD Stent System is available in three stent models, each engineered for specific diameters to provide consistent stent-to-artery ratios across the range of reference vessel diameters indicated:

- Small Vessel (SV): 2.25 mm, 2.50 mm and 2.75 mm
- Workhorse (WH): 3.00 mm, 3.50 mm
- Large Vessel (LV): 4.00 mm, 4.50 mm and 5.00 mm

Contents for (1) SYNERGY XD Monorail Stent System

• One (1) SYNERGY XD Monorail Stent System
• One (1) Flushing needle with luer fitting

2.4 Drug Component Description

The stent component of the SYNERGY XD Stent System is a PtCr stent with a drug/polymer coating. The coating is comprised of a bioabsorbable polymer matrix that contains an active pharmaceutical ingredient (everolimus). This is the same active pharmaceutical ingredient as is used in PROMUS™ (XIENCE V™) and the existing SYNERGY matrix.
See Section 2.4.1 Everolimus and 2.4.2 Polymer Carrier sections for descriptions of drug and polymer, respectively.

2.4.1 Everolimus

The active pharmaceutical ingredient in the SYNERGY XD Stent is everolimus. The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and its chemical structure is provided in Figure 2.1.

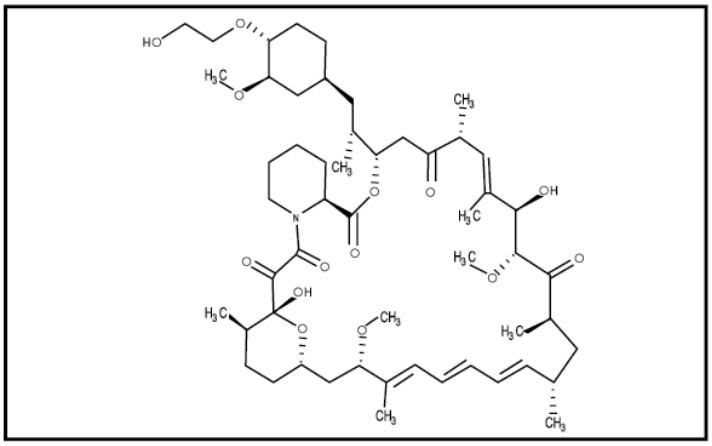

Figure 2.1 The Chemical Structure of Everolimus

2.4.2 Polymer Carrier

The SYNERGY XD Stent is coated on the abluminal stent surface (surface in contact with vessel wall) with a bioabsorbable drug matrix. The bioabsorbable drug matrix is composed of PLGA [poly (DL-lactide-co-glycolide)] mixed with everolimus. The chemical structure of PLGA is shown below in Figure 2.2. In vivo studies support that the polymer degradation is essentially complete by 4 months.

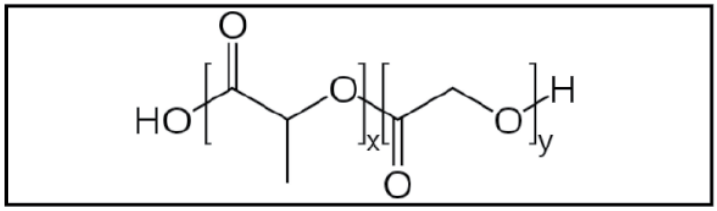

Figure 2.2 The Chemical Structure of PLGA

2.4.3 Product Matrix and Everolimus Content

Table 2.2 SYNERGY™ XD Stent System Product Matrix and Everolimus Content

Product Code	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
H7493941808220	2.25	8	38.9
H7493941808250	2.50	8	38.9
H7493941808270	2.75	8	38.9
H7493941808300	3.00	8	46.5
H7493941808350	3.50	8	46.5
H7493941808400	4.00	8	67.5
H7493941812220	2.25	12	58.3
H7493941812250	2.50	12	58.3
H7493941812270	2.75	12	58.3
H7493941812300	3.00	12	66.3
H7493941812350	3.50	12	66.3
H7493941812400	4.00	12	96.2
H7493941812450	4.50	12	96.2
H7493941812500	5.00	12	96.2
H7493941816220	2.25	16	77.6
H7493941816250	2.50	16	77.6
H7493941816270	2.75	16	77.6
H7493941816300	3.00	16	92.7
H7493941816350	3.50	16	92.7
H7493941816400	4.00	16	124.8
H7493941816450	4.50	16	124.8
H7493941816500	5.00	16	124.8
H7493941820220	2.25	20	96.9
H7493941820250	2.50	20	96.9
H7493941820270	2.75	20	96.9
H7493941820300	3.00	20	112.5
H7493941820350	3.50	20	112.5
H7493941820400	4.00	20	153.5
H7493941820450	4.50	20	153.5
H7493941820500	5.00	20	153.5
H7493941824220	2.25	24	121.1
H7493941824250	2.50	24	121.1
H7493941824270	2.75	24	121.1
H7493941824300	3.00	24	132.3
H7493941824350	3.50	24	132.3
H7493941824400	4.00	24	182.2
H7493941824450	4.50	24	182.2
H7493941824500	5.00	24	182.2
H7493941828220	2.25	28	140.5
H7493941828250	2.50	28	140.5
H7493941828270	2.75	28	140.5
H7493941828300	3.00	28	158.7
H7493941828350	3.50	28	158.7
H7493941828400	4.00	28	210.8
H7493941828450	4.50	28	210.8
H7493941828500	5.00	28	210.8
H7493941832220	2.25	32	159.8
H7493941832250	2.50	32	159.8
H7493941832270	2.75	32	159.8

H7493941832300	3.00	32	178.5
H7493941832350	3.50	32	178.5
H7493941832400	4.00	32	239.5
H7493941832450	4.50	32	239.5
H7493941832500	5.00	32	239.5
H7493941838220	2.25	38	188.9
H7493941838250	2.50	38	188.9
H7493941838270	2.75	38	188.9
H7493941838300	3.00	38	211.6
H7493941838350	3.50	38	211.6
H7493941838400	4.00	38	287.2
H7493941848250	2.50	48	237.2
H7493941848270	2.75	48	237.2
H7493941848300	3.00	48	271.0
H7493941848350	3.50	48	271.0
H7493941848400	4.00	48	363.6

3 INTENDED USE/INDICATIONS FOR USE

The SYNERGY XD Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients, including those with diabetes mellitus, 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 ≤5.00 mm in diameter in lesions ≤ 44 mm in length and for high bleeding risk patients with coronary arteries ≥2.25 mm to ≤5.00 mm in diameter in lesions ≤34 mm in length.

4 CONTRAINDICATIONS

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

- 316L stainless steel, platinum, chromium, iron, nickel or molybdenum
- Everolimus or structurally-related compounds
- The polymer or their individual components (see Section 2.4.2 Polymer Carrier)

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 (see Section 6.2, Pre- and Post- Procedure Antiplatelet Regimen for more information).

5 WARNINGS

- To maintain sterility, the package should not be opened or damaged prior to use.
- The use of this product carries the risks associated with coronary artery stenting, including stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

6 PRECAUTIONS

6.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery is readily available.
- Subsequent stent blockage may require repeat dilation of the arterial segment containing the stent. The long-term outcome following repeat dilation of endothelialized stents is not well characterized.
- Careful consideration should be given to the risks and benefits of use in patients with history of severe reaction to contrast agents.
- Do not expose the delivery system to organic solvents such as alcohol or detergents.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment and balloon withdrawal. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system, visually confirm complete balloon deflation under fluoroscopy. Failure to do so may cause increased SDS withdrawal forces and result in guide catheter movement into the vessel and subsequent arterial damage.

- Stent thrombosis is a rare event and is frequently associated with myocardial infarction (MI) or death. In the clinical trials analyzed to date, differences in the incidence of stent thrombosis have not been associated with an increased risk of cardiac death, MI, or all-cause mortality.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed during the EVOLVE clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI or death. When treating such patients, physicians should be aware of this increased risk and consider available data and the limitations of such data.
- Orally-administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglyceride levels.

SYNERGY XD leverages the clinical data from the EVOLVE Clinical Trial Program. Therefore, the statements below regarding SYNERGY also apply to SYNERGY XD.

6.2 Pre- and Post-Procedure Antiplatelet Regimen

In the EVOLVE II Trial, a $P2Y_{12}$ inhibitor was administered pre-procedure and for a period of 6 months post procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with the $P2Y_{12}$ inhibitor and was required to be continued indefinitely to reduce the risk of thrombosis.

The optimal duration of antiplatelet therapy, specifically $P2Y_{12}$ inhibitor therapy, is unknown and DES thrombosis may still occur despite continuation of therapy beyond current professional society guidelines. Data from several studies suggest that a longer duration of antiplatelet therapy than was recommended post-procedurally in DES pivotal clinical trials may be beneficial. Provided herein are recommendations for post-procedural antiplatelet therapy from the 2016 ACC/AHA/SCAI Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease; see Section 6.2.1, Oral Antiplatelet Therapy.

6.2.1 Oral Antiplatelet Therapy

Continuation of combination treatment with aspirin and a $P2Y_{12}$ inhibitor after PCI appears to reduce major adverse cardiac events. On the basis of randomized clinical trials, the 2016 ACC/AHA guidelines recommend aspirin 81 mg daily be given indefinitely after PCI. In patients who are not at high risk of bleeding, a $P2Y_{12}$ inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in acute coronary syndrome (ACS) patients.

Full guidelines are provided at the following website: http://www.onlinejacc.org

Consistent with the 2016 ACC/AHA guidelines,[1] and the DAPT Study,[2] longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk. In patients who are at a high risk of bleeding or who develop significant bleeding during DAPT treatment, these guidelines suggest that a shorter DAPT duration may be reasonable.

Based upon the results of the EVOLVE Short DAPT Study the SYNERGY XD stent can be safely used in conjunction with shortened DAPT in patients at high risk for bleeding. In the EVOLVE Short DAPT Study, high bleeding risk subjects were defined as meeting one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/µL. Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, ischemic and bleeding risks, and patient preference.

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Generally, it is recommended to postpone elective surgery for one year and among those patients for whom surgery cannot be deferred, ASA should be considered during the perioperative period in high risk DES patients.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

[1] Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2016;68:1082 -1115.
[2] Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. N Engl J Med. 2014; 371:2155-66.

6.3 Longitudinal Stent Deformation

Longitudinal stent deformation is a recognized potential failure mode of thin strut coronary stents.[3] Crossing a newly deployed stent with a second device, such as a balloon catheter, stent system or IVUS catheter, can lead to the second device transmitting force to the implanted stent. In this situation, if the second device is advanced or retracted, longitudinal stent deformation (i.e., longitudinal compression or elongation) of the implanted stent may occur. Although a rare event, longitudinal stent deformation may result in adverse clinical events and/or the need for additional treatment including repeat dilation of the implanted stent, placement of a second stent, and/or surgical intervention.

An analysis of complaint reports suggests that coronary artery calcification, vessel tortuosity, and stent malapposition in conjunction with crossing a newly deployed stent with an ancillary device may be associated with an increased risk of longitudinal stent deformation. Implantation techniques that may reduce the likelihood of procedure related complications, including stent deformation, are described in the appropriate sections of this DFU (see Sections 14.3.4 Delivery Procedure, 14.3.5 Deployment Procedure, 14.3.6 Removal Procedure and Post-Deployment Dilation of Stented Segment).

[3] Hanratty CG, Walsh SJ. Longitudinal Compression: A "new" Complication with Modern Coronary Stent Platforms - Time to Think Beyond Deliverability? Eurointervention 2011;7:872-877.

6.4 Use of Multiple Stents

In the EVOLVE Clinical Program, the protocols specified that lesions were to be treated with no more than one stent, except in situations involving bailout stenting. The use of multiple DES will expose the patient to larger amounts of drug and polymer. When more than one stent is required, resulting in stent-to-stent contact, stent materials should be of similar composition to avoid the possibility of corrosion due to the presence of dissimilar metals in a conducting medium. Potential interactions of the SYNERGY Stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

6.5 Brachytherapy

The safety and effectiveness of the SYNERGY Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in a SYNERGY Stent have not been established. Both vascular brachytherapy and the SYNERGY Stent alter arterial remodeling. The interaction between these two treatments has not been determined.

6.6 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices or laser angioplasty catheters in conjunction with an implanted SYNERGY Stent have not been established.

6.7 Use in Special Populations

6.7.1 Pregnancy

Pregnancy "Category C". See Section 7.5, Pregnancy. The SYNERGY™ Stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a SYNERGY Stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time. There are also potential risks to the fetus due to the ionizing radiation required for visualization during PCI procedures.

6.7.2 Lactation

See Section 7.6, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent for the mother.

6.7.3 Gender

See Clinical Information – Section 10, Clinical Studies. Clinical studies of the SYNERGY Stent were not powered to study safety or effectiveness of the SYNERGY Stent in sex-specific subgroups, however exploratory analyses were performed.

6.7.4 Ethnicity

See Clinical Information – Section 10, Clinical Studies. Clinical studies of the SYNERGY Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity, either by individual category or when grouped by Caucasian and non-Caucasian.

6.7.5 Pediatric Use

The safety and effectiveness of the SYNERGY Stent in pediatric patients have not been established.

6.7.6 Geriatric Use

Clinical studies of the SYNERGY Stent did not have an upper age limit. Among the 846/1684 patients treated with the SYNERGY Stent in the EVOLVE II Randomized controlled study, 407 patients were age 65 or older and 46 patients were age 80 or older. A post hoc analysis of patients treated with the SYNERGY Stent showed no significant differences in 12 month clinical outcomes (primary endpoint of target lesion failure) between patients under age 65 and those age 65 or older.

6.8 Lesion/Vessel Characteristics

The safety and effectiveness of the SYNERGY Stent have not been established in the cerebral, carotid, or peripheral vasculature or in the following patient populations:

- Patients with vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameters <2.25 or >5.00 mm.
- Patients with coronary artery lesions longer than 44 mm or requiring more than one SYNERGY Stent.
- Patients with lesions located in saphenous vein grafts, in the left main coronary artery, ostial location, or complex bifurcation (e.g. bifurcation lesion requiring treatment with more than one stent).
- Patients with diffuse disease or reduced blood flow distal to the identified lesions.
- Patients with a recent acute ST elevation myocardial infarction where there is evidence of thrombus or poor flow.
- Patients with in-stent restenosis.
- Patients with a chronic total occlusion.
- Patients with 3 vessel disease.

6.9 Drug Interactions

See Section 7.3, Drug Interactions. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the SYNERGY Stent because of limited systemic exposure to everolimus eluted from SYNERGY Stent used in the EVOLVE clinical trials (see Section 7.2, Pharmacokinetics). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place a SYNERGY XD Stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a SYNERGY XD Stent.

6.10 Immune Suppression Potential

Everolimus, the active drug component of the SYNERGY XD Stent, is an immunosuppressive agent. Immune suppression as a result of everolimus exposure was not observed in the EVOLVE Clinical Program. However, for patients who receive several SYNERGY XD Stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

6.11 Lipid Elevation Potential

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low- and high-dose prolonged oral therapy in a dose-related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the SYNERGY XD Stent is expected to be significantly lower than concentrations usually obtained in transplant patients.

6.12 Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that the SYNERGY XD Stent is MR Conditional for single and overlapped conditions up to 94 mm. A patient with this device can be safely scanned in a Magnetic Resonance system meeting the following conditions:

- 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)

Under the scan conditions defined above, the SYNERGY XD Stent is expected to produce a maximum temperature rise of 5ºC or less after 15 minutes of continuous scanning.

MR Image quality may be compromised if the area of interest is within the lumen or relatively near the stent. Therefore, it may be necessary to optimize MR imaging parameters for the presence of the stent. The image artifact extends approximately 1 cm from the stent when scanned in non-clinical MR testing specified in ASTM F2119-07. The artifact does obscure the device lumen. Image artifact was minimized using the spin echo sequence versus gradient echo.

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.

Magnetic Resonance
Conditional

6.13 Stent Handling (also see Section 14, Operational Instructions)

• For single use only. Do not resterilize or reuse this product. Note product “Use By” date. (see Section 1, Warning)

• The premounted SYNERGY XD Stent and its delivery system are designed for use as a unit. The stent is not to be removed from its delivery balloon. The stent is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and coating and/or lead to stent embolization.

• Special care must be taken not to handle or in any way disrupt the stent position on the delivery balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through hemostasis valve adapter and guide catheter hub.

• Excessive manipulation or handling may cause coating damage, contamination, or dislodgment of the stent from the delivery balloon.

• Use only the appropriate balloon inflation media (see Section 14.3.3, Balloon Preparation). Do not use air or any gas medium to inflate the balloon.

• In the event the SYNERGY XD Stent is deployed or damaged, do not use the product and contact your local Boston Scientific Representative for return information.

6.14 Stent Placement

Preparation

• Do not prepare or pre-inflate balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 14.3.3, Balloon Preparation.

• The vessel should be pre-dilated with an appropriately sized balloon. Failure to do so may increase the risk of placement difficulty and procedural complications.

• If unusual resistance is felt at any time during lesion access before stent implantation see Section 6.15, Stent Delivery System Removal.

• An unexpanded stent should be introduced into the coronary arteries one time only. An unexpanded stent should not be subsequently moved in and out through the distal end of the guide catheter as stent or coating damage or stent dislodgment from the balloon may occur.

Placement

• Do not expand the stent if it is not properly positioned in the vessel (see Section 6.15, Stent Delivery System Removal).

• Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Section 14.4, In Vitro Information, Table 14.1, Typical SYNERGY XD Stent System Compliance). Use of pressures higher than specified on product label may result in a ruptured balloon and intimal damage and dissection.

• The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.

• Stent placement may potentially compromise side branch patency.

• Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion, and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, repeat dilation, placement of additional stents, or other).

• When treating multiple lesions, the distal lesion should generally be stented first, followed by stenting of the more proximal lesion(s). Stenting in this order alleviates the need to cross the proximal stent in placement of the distal stent and reduces the chances of dislodging or damaging the proximal stent.

6.15 Stent Delivery System Removal

- Following stent placement, confirm complete balloon deflation. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
- If unusual resistance is felt at any time during lesion access before stent implantation, the stent delivery system and the guide catheter should be removed as a single unit.
- Retraction of an unexpanded stent back into the guide catheter could result in stent or coating damage or stent dislodgment from the balloon. If retraction of the unexpanded stent back into the guide catheter is required, ensure that the guide catheter is coaxially aligned with the stent system and cautiously withdraw the stent system into the guide catheter under direct fluoroscopic visualization.
- Stent retrieval methods (use of additional wires, snares and/ or forceps) may result in additional trauma to the vascular access site. Complications can include bleeding, hematoma, or pseudoaneurysm.

Note: When removing the entire stent delivery system and guide catheter as a single unit, the following steps should be executed under direct fluoroscopic visualization.

- If greater than usual resistance is felt during delivery system withdrawal, pay particular attention to guide catheter position. In some cases, it may be necessary to pull back slightly on the guide catheter in order to prevent deep seating (unplanned advancement) of the guide catheter and subsequent vessel damage. In

cases where planned guide catheter movement has occurred, angiographic assessment of the coronary tree should be undertaken to ensure that there is no damage to the coronary vasculature.

- Following stent placement confirm complete balloon deflation. Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 30 seconds, for balloon deflation. Larger and longer balloons may require more time for deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
- Maintain guidewire placement across the lesion during the entire removal process. Carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is just distal to the guide catheter distal tip.
- The stent delivery system and the guide catheter should be pulled back until the tip of the guide catheter is just distal to the arterial sheath, allowing the guide catheter to straighten. Carefully retract the stent delivery system into the guide catheter and remove the stent delivery system and the guide catheter from the patient as a single unit while leaving the guidewire across the lesion.

Failure to follow these steps, and/or applying excessive force to the stent delivery system, can potentially result in stent or coating damage, stent dislodgment from the balloon, and/or damage to the delivery system.

6.16 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- In the EVOLVE Clinical program, a $P2Y_{12}$ inhibitor was administered pre-procedure and for a period of 6 months post-procedure and for 12 months in patients who were not at high risk of bleeding. Aspirin was administered concomitantly with a $P2Y_{12}$ inhibitor and then continued indefinitely to reduce the risk of thrombosis. See Section 10, Clinical Studies, for more specific information.
- If the patient requires MRI imaging, see Section 6.12, Magnetic Resonance Imaging (MRI).

7 DRUG INFORMATION

7.1 Mechanism of Action

The mechanism by which the SYNERGY™ XD Stent inhibits neointimal growth as seen in pre-clinical studies has been established.[4] At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

[4] Lavigne, MC, Grimsby, JL, Eppihimer, MJ. J Cardiovasc Pharmacol. 2012;59:165-174

7.2 Pharmacokinetics

Everolimus Pharmacokinetics (PK) when eluted from the SYNERGY XD Stent post-implantation has 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. Whole blood everolimus PK parameters determined from patients receiving the SYNERGY Stent are provided in Table 7.1.

Table 7.1 Whole Blood Everolimus Pharmacokinetic Parameters (Mean ± SD) for SYNERGY (Groups with Three or More Patients) Following SYNERGY Stent Implantation.

Pharmacokinetic Parameter**	All Subjects		
	58 µg [b]	113 µg [c]	189 µg
N	3 [c]	3 [b]	4 [b]
t_{max} (h)	0.90 ± 0.36	0.48 ± 0.08	0.48 ± 0.03
C_{max} (ng/mL)	0.31 ± 0.07	0.35 ± 0.04	0.84 ± 0.41
AUC_{0-t} (ng•h/mL)	0.32 ± 0.25	0.56 ± 0.47	8.50 ± 3.91
AUC_{0-24h} (ng•h/mL)	0.32 ± 0.25	0.56 ± 0.47	6.73 ± 2.10
$AUC_{0-\infty}$ [a] (ng•h/mL)	NA	NA	47.81 ± 61.50
$t_{1/2term}$ [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
[a]: Accurate determination not possible
[b]: n=0 for $AUC_{0-\infty}$, $t_{1/2\ term}$ and CL
[c]: n=1 for $AUC_{0-\infty}$, $t_{1/2\ term}$ and CL
t_{max} (h)= time to maximum concentration
C_{max}= maximum observed blood concentration
$t_{1/2}$ (h)= terminal phase half-life
AUC_{0-t} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
AUC_{0-24h} = the area beneath the blood concentration versus time curve: time zero to 24 hours post-implant
$AUC_{0-\infty}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL= total blood clearance
**Dose-normalized C_{max} and AUC_{0-24h} were plotted versus total dose. Across the dose range (58 to 257 µg), the plots showed that the data from the individual subjects are evenly distributed around the median values.

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 $t_{1/2\ term}$ and $AUC_{0-\infty}$ 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 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.

7.3 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 SYNERGY Stent because of limited systemic exposure to everolimus eluted from SYNERGY (see Section 6.9, Drug Interactions and Section 7.2, Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the SYNERGY Stent in a patient taking a drug with known interaction with everolimus.

The amount of drug that circulates in the bloodstream following implantation of a SYNERGY Stent is significantly lower than that obtained with oral doses. Everolimus, when prescribed as an oral medication in systemic doses, may interact with the drugs/foods listed below. Medications that are strong inhibitors of CYP3A4 or PgP might reduce everolimus metabolism in vivo. Hence, co-administration of strong inhibitors of CYP3A4 or PgP may increase the blood concentrations of everolimus.

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

Zortress™, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day. Outside the U.S., Zortress is sold under the brand name, Certican™, in more than 70 countries. Everolimus is also approved in the United States under the name of

Afinitor™ for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the bloodstream following implantation of a SYNERGY Stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day), see Section 7.2, Pharmacokinetics.

7.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

SYNERGY XD Stent is made of platinum chromium alloy which consists of platinum, chromium, iron, nickel, and molybdenum, and contains the drug everolimus in a similar amount as PROMUS™ (XIENCE V™). Therefore the previous testing conducted on such devices is also applicable for SYNERGY XD as described below.

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of PROMUS (XIENCE V) everolimus eluting stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group PROMUS (XIENCE V) Stent. The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group.

Based on the results of this study, the PROMUS (XIENCE V) Stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

SYNERGY Stent was evaluated for genotoxicity using Ames bacterial mutagenicity assay, in vitro gene mutation assay in mammalian cells (mouse lymphoma) at thymidine kinase loci and mouse bone marrow micronucleus assay. The results from these in vitro and in vivo studies showed that SYNERGY Stents are not mutagenic and non-genotoxic in nature. In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of PROMUS (XIENCE V) Stent in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. There was no statistical difference between the test article PROMUS (XIENCE V) Stent and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in-utero mortality. Additionally, the PROMUS (XIENCE V) Stent did not cause any reproductive toxicity in the offspring in this study.

The SYNERGY Stent also has a bioabsorbable polymer coating PLGA which is known to degrade by hydrolysis into lactic and glycolic acid and ultimately metabolized into carbon dioxide and water. PLGA is being used as part of medical devices and also as a drug delivery agent for many years. There are no known genotoxic, carcinogenic or reproductive toxicity effects of PLGA in published literature.

7.5 Pregnancy

Pregnancy “Category C”: There are no everolimus or SYNERGY XD Stent related studies in pregnant women. Effects of a similar stent (PROMUS/XIENCE V) on prenatal and postnatal rat development were not different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a SYNERGY XD Stent and continued for one year post-implantation. The SYNERGY XD Stent should be used in pregnant women only if the potential benefits justify the potential risks.

Safety of the SYNERGY XD Stent has not been evaluated in males intending to father children.

7.6 Lactation

It is not known whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to SYNERGY™ XD Stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternative percutaneous coronary intervention procedure.

8 OVERVIEW OF CLINICAL STUDIES

The principal safety and effectiveness for the SYNERGY XD Stent System is leveraged from the global EVOLVE Clinical Trial Program, a series of clinical trials conducted on the similar SYNERGY Stent System.

The EVOLVE Clinical Program evaluates the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of atherosclerotic lesions. The Program includes the EVOLVE (First Human Use) trial and the EVOLVE II study, which comprises a 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. Following commercialization, post-market clinical studies have been conducted to evaluate the safety and effectiveness of the 48 mmm length stent and also shortened dual antiplatelet therapy following SYNERGY stent implantation in specific patient subsets, for stent lengths up to 38 mm. The EVOLVE Short DAPT Study was conducted to evaluate the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent System. A summary of the EVOLVE, EVOLVE II RCT, PK, DM, QCA, EVOLVE 48 and EVOLVE Short DAPT trial designs are presented in Table 8.1.

8.1 EVOLVE Clinical Trial

EVOLVE is a prospective, randomized, multicenter single blind non-inferiority study designed to evaluate clinical, angiographic and IVUS outcomes for the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System compared to PROMUS Element™ Stent in the treatment of subjects with atherosclerotic lesions ≤28 mm in length (by visual estimate) in *de novo* coronary arteries ≥2.25 mm to ≤3.50 mm in diameter (by visual estimate).

The primary clinical endpoint was the 30-day target lesion failure (TLF) rate defined as a composite of cardiac death or myocardial infarction (MI) related to the target vessel, or ischemia-driven target lesion revascularization (TLR). The primary angiographic endpoint was in-stent late loss as measured by QCA at 6 months.

A total of 291 patients were enrolled at 29 sites in Europe and Asia-Pacific region (Australia and New Zealand). The protocol mandated antiplatelet therapy compliance in accordance with the 2007 ACC/AHA/SCAI Guidelines for PCI.[5]

The study is now complete including follow-up through 5 years.

[5] King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. Circulation. 2008; 117:261–295.

8.2 EVOLVE II Clinical Trial

8.2.1 Randomized Controlled Trial (RCT)

The EVOLVE II RCT is a prospective, randomized (1:1), controlled, single-blind, multi-center, 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. To be eligible for enrollment, patients had to have silent ischemia, stable angina, unstable angina or non-ST elevation myocardial infarction (NSTEMI); ST elevation MI (STEMI) was an exclusion criterion. Predilation was required by the study protocol, patients pre-treated with rotational or directional atherectomy or cutting/scoring balloons were eligible for enrollment. Patients with bifurcation lesions where treatment with a single stent was planned were eligible while those with bifurcation lesions where treatment with two stents was planned were not eligible. Saphenous vein graft lesions, in-stent restenosis and lesions in the left main coronary artery were also excluded.

The primary endpoint was the rate of TLF, defined as any ischemia-driven TLR, MI 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.

A total of 1684 patients (846 SYNERGY Stent and 838 PROMUS Element Plus Stent) were randomized and enrolled at 125 sites in 16 countries in the Asia-Pacific region, Europe, Japan, Canada and the United States. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/SCAI Guidelines for PCI.[6]

The study is now complete including follow-up through 5 years.

[6] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651.

8.2.2 Pharmacokinetics (PK) Sub-study

EVOLVE II PK is a prospective, single-arm, multi-center, observational sub-study of the EVOLVE II Trial to evaluate everolimus blood levels following stent implantation in patients who undergo treatment with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System.

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. A total of 21 patients were enrolled at 2 sites in the United States and 4 sites in Japan. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/ SCAI Guidelines for PCI.[7] Clinical follow-up is complete through 5 years. See Section 7.2, Pharmacokinetics.

[7] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651.

8.2.3 Diabetic (DM) Sub-study

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 Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of coronary lesions in patients with medically treated diabetes mellitus. 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.

The primary endpoint was the rate of TLF at 12 months post-index procedure, compared to a performance goal based on historical everolimus-eluting stent results based on subjects with diabetes.

The EVOLVE II DM sub-study pooled: 1) diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patients) with 2) diabetic subjects enrolled in the non-randomized Diabetes single-arm study (203 patients from 48 sites in Asia-Pacific region, Europe, Canada and the United States), following completion of EVOLVE II RCT enrollment. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/SCAI Guidelines for PCI.[8]

The sub-study is now complete including follow-up thorough 5 years.

[8] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011;124:e574-e651

8.3 EVOLVE II Quantitative Coronary Angiography (QCA) Trial

EVOLVE II QCA is a prospective, single-arm, multi-center, observational study designed to evaluate clinical, angiographic and IVUS outcomes in atherosclerotic coronary lesions treated with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. Patients with 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. The primary endpoint was in-stent late loss at 9 months post-procedure as measured by quantitative coronary angiography (QCA). All patients were required to undergo 9 month angiography and IVUS assessments. The 9 month in-stent late loss performance goal was based on historical PLATINUM QCA and the PROMUS arm of RESOLUTE all-comers results.

A total of 100 patients were enrolled at 12 sites in Australia, Japan, New Zealand, and Singapore. The protocol mandated antiplatelet therapy compliance in accordance with the 2011 ACC/AHA/ SCAI Guidelines for PCI.[9] The study is complete.

[9] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

8.4 EVOLVE 48

The EVOLVE 48 Study is a prospective, multicenter, open label, single-arm study to assess the safety and effectiveness of the SYNERGY 48 mm stent for the treatment of atherosclerotic lesion(s). Subjects received the SYNERGY 48 mm stent for treatment of native coronary artery with a reference vessel diameter ≥2.50 mm and ≤4.00 mm and lesion length >34 mm and ≤44 mm (both by visual estimate). The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, 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.

A total of 100 patients were enrolled at 15 sites in United States, Europe and New Zealand. Clinical follow up is ongoing to 2 years.

The SYNERGY 48 mm stent has been commercialized in Sweden since February 2017, and data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) provides real world evidence on the outcomes in an unselected population. The registry provides extensive data from all 29 centers in Sweden that perform PCI. A 500-patient cohort of patients treated with the SYNERGY 48 mm stent, and no other non-SYNERGY stents, who had follow-up through 1-year was identified. Clinical outcomes of death, myocardial infarctions, revascularizations and stent thromboses assessed from this cohort.

8.5 EVOLVE Short DAPT Study

The EVOLVE Short DAPT Study* is a prospective, multi-center, single-arm study in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent. A historical control and a propensity score approach was used to assess the safety of 3-month DAPT in high bleeding risk patients. High bleeding risk subjects were enrolled if they met one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL. Subjects were prescribed dual antiplatelet therapy ($P2Y_{12}$ inhibitor + aspirin) between 0-3 months post-procedure. Aspirin was optional between 0-3 months for subjects on chronic anticoagulation. Subjects were eligible to discontinue $P2Y_{12}$ inhibitor at 3 months if they were compliant with the prescribed dual antiplatelet therapy and were free from events between 0-3 months (stent thrombosis, myocardial infarction, revascularization, or stroke). Subjects that discontinued $P2Y_{12}$ inhibitor at 3-months were prescribed aspirin through the end of study. The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or MI, and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis related to SYNERGY. The pre-specified secondary endpoint was the rate of BARC 2,3,5 Bleeding** between 3-15 months. A total of 2,009 patients were enrolled at 110 sites in the United States, Europe, Brazil and Japan, of which 1,487 patients were eligible to and discontinued $P2Y_{12}$ inhibitor at 3-months. Patients were followed at 3, 6, 12- and 15-months post-index procedure. The study is considered complete with follow-up through 15-months.

* Mauri L, Kirtane AJ, Windecker S, et al. Am Heart J. 2018;205:110–117.

**Mehran R, Rao SV, Bhatt DL et al. Circulation 2011;123:2736-2747.

Table 8.1 Comparison of EVOLVE Clinical Studies

	EVOLVE	EVOLVE II				EVOLVE 48	EVOLVE SHORT DAPT
		RCT	DM	PK	QCA		
Purpose	Evaluation of safety and effectiveness in native *de novo* coronary lesions	Evaluation of safety and effectiveness in native coronary lesions	Evaluation of safety and effectiveness in native coronary lesions in patients with medically treated diabetes mellitus	Evaluation of everolimus blood levels	Evaluation of angiographic and IVUS outcomes in native coronary lesions	Evaluation of safety and effectiveness of SYNERGY 48 mm stent	Evaluation of safety of 3-month DAPT in subjects at high risk for bleeding*** receiving SYNERGY
Study Design	Prospective, randomized, controlled, multi-center, single-blind non-inferiority to PROMUS Element™	Prospective, randomized, controlled, multi-center, single-blind non-inferiority to PROMUS Element™ Plus	Prospective, single arm, multi-center, comparison to performance goal	Prospective, single arm, multicenter, observational study	Prospective, single arm, multi-center, observational study	Prospective, open label, single arm, multi-center study	Prospective, multi-center, single arm, historical control, propensity score approach
Primary Endpoint(s)	30 Day TLF 6 month In-stent late loss	12 month TLF	12 month TLF	N/A, observational	9 month In-stent late loss	12 month TLF	Co-Primary Endpoints (3-15 months): 1,) death/MI; 2.) ARC definite/probable ST related to SYNERGY
Number of Patients (ITT)	291 SYNERGY™ Full dose: 94 SYNERGY ½ dose: 99 PROMUS Element: 98	1684 SYNERGY: 846 PROMUS Element Plus: 838	203 SYNERGY	21 SYNERGY	100 SYNERGY	100 SYNERGY 48 mm	2009 SYNERGY
Lesion Criteria: Vessel Diameter (by visual estimate), mm	≥2.25 to ≤3.50	≥2.25 to ≤4.00				≥2.50 to ≤4.00	No Restriction
Lesion Criteria: Lesion Length (by visual estimate), mm	≤28	≤34				≤ 44	No Restriction

Total Target Lesions	1	Up to 3 in 2 epicardial vessels		1	No Restriction
Stent Matrix, mm	Diameter: 2.25, 2.50, 2.75, 3.00, 3.50 Length: 8, 20, 32	Diameter: 2.25, 2.50, 3.00, 3.50, 4.00 Length: 8, 12, 20, 28, 32/38*		Diameter: 2.50, 2.75 **, 3.00, 3.50, 4.00 Length: 48	Diameter: 2.25, 2.50, 3.00, 3.50, 4.00 Length: 8, 12, 20, 28, 32, 38
Post-Procedure Antiplatelet Therapy	A thienopyridine for at least 6 months, ideally for 12 months in patients who were not at high risk of bleeding. ASA: indefinitely	A $P2Y_{12}$ inhibitor for at least 6 months, ideally for 12 months in patients who were not at high risk of bleeding. ASA: indefinitely		A $P2Y_{12}$ inhibitor for at least 6 months, ideally for 12 months in patients who were not at high risk of bleeding. ASA: indefinitely	P2Y12 inhibitor + ASA for 3-months, then ASA 3-15 months. For subjects on anticoagulation, ASA option 0-3 months.
Follow-Up	Clinical: 30 days, 6 months, 9 months 1 year, annually 2 – 5 years Angiographic: 6 months IVUS: 6 months	Clinical: 30 days, 6 months, 1 year, 18 months, annually 2 – 5 years	Clinical: 30 days, 9 months, 1 year, Angiographic: 9 month, IVUS: 9 month	Clinical: 30 days, 6 months, 1 year and 2 years	Clinical: 3 months, 6 months, 1 year and 15 months
	* 2.25 x 38 mm is only available in the SYNERGY test matrix and 2.25 x 32 is only available in the PROMUS Element Plus control matrix. ** 2.75 x 48 mm was not included in the investigational device matrix in the United States (US) ***In the EVOLVE Short DAPT Study, high bleeding risk subjects were defined as meeting one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL Abbreviations: ASA=aspirin; BMS=bare-metal stent; DAPT= dual antiplatelet therapy; DM=diabetes mellitus; IVUS=intravascular ultrasound; MI=myocardial infarction; PK=pharmacokinetics; QCA=quantitative coronary angiography; RCT=randomized controlled trial; TLF=target lesion failure, TLR=target lesion revascularization.				

9 ADVERSE EVENTS

9.1 Observed Adverse Events

Observed adverse event experience comes from EVOLVE, EVOLVE II RCT, EVOLVE II DM, EVOLVE II QCA, EVOLVE 48, and the EVOLVE Short DAPT Study. Major clinical events for these studies are shown in Table 9.1.

Table 9.1 EVOLVE II RCT and DM Sub-study Major Clinical Events From Post-Procedure to 5 year, EVOLVE II QCA Major Clinical Events From Post-Procedure to 9 month Follow-Up, EVOLVE From Post-Procedure to 5 year Follow-Up, EVOLVE 48 From Post-Procedure to 12 Month Follow-Up and EVOLVE Short DAPT Study From Post-Procedure to 15-Month Follow-up.

	EVOLVE II RCT		EVOLVE II DM	EVOLVE II QCA	EVOLVE	EVOLVE 48	EVOLVE SHORT DAPT		
	SYNERGY™ (N=846)*	PROMUS Element™ Plus[1] (N=838)*	SYNERGY (N=466)*	SYNERGY (N=100)*	SYNERGY (N=94)*	SYNERGY 48 mm (N=100)	SYNERGY (N=2,009)	3-Month DAPT SYNERGY (N=1,487)	Non 3-Month DAPT SYNERGY (N=522)
In-Hospital All death, MI, TVR	3.9% (33/846)	3.9% (33/838)	3.2% (15/466)	5.0% (5/100)	1.1% (1/94)	0.0% (0/100)	0.5% (10/2009)****	0.0% (0/1487)****	1.9% (10/522)****
All Death	0.0% (0/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.1% (3/2009)	0.0% (0/1487)	0.6% (3/522)
Cardiac Death	0.0% (0/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.1% (2/2009)	0.0% (0/1487)	0.4% (2/522)
Non-cardiac Death	0.0% (0/846)	0.0% (0/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
MI	3.5% (30/846)**	3.8% (32/838)**	3.0% (14/466)**	5.0% (5/100)**	1.1% (1/94)***	0.0% (0/100)****	0.4% (9/2009)	0.0% (0/1487)	1.7% (9/522)
Q-Wave MI	0.1% (1/846)	0.0% (0/838)	0.4% (2/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
Non-Q-Wave MI	3.4% (29/846)	3.8% (32/838)	2.6% (12/466)	5.0% (5/100)	1.1% (1/94)	0.0% (0/100)	0.4% (9/2009)	0.0% (0/1487)	1.7% (9/522)
Cardiac death or MI	3.5% (30/846)	3.8% (32/838)	3.0% (14/466)	5.0% (5/100)	1.1% (1/94)	0.0% (0/100)	0.5% (10/2009)	0.0% (0/1487)	1.9% (10/522)
TVR	0.5% (4/846)	0.1% (1/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
TLR	0.4% (3/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
Non-TLR	0.1% (1/846)	0.1% (1/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
30-Day All death, MI, TVR	4.3% (36/846)	5.0% (42/833)	3.9% (18/466)	5.0% (5/100)	1.1% (1/93)	0.0% (0/100)	1.4% (27/1995)****	0.0% (0/1487)****	5.3% (27/508)****
9 month All death, MI, TVR				8.0% (8/100)	5.4% (5/93)				
All Death				0.0% (0/100)	1.1% (1/93)				
Cardiac Death				0.0% (0/100)	0.0% (0/93)				
Non-cardiac Death				0.0% (0/100)	1.1% (1/93)				
MI				5.0% (5/100)**	1.1% (1/93)***				
Q-Wave MI				0.0% (0/100)	0.0% (0/93)				
Non-Q-Wave MI				5.0% (5/100)	1.1% (1/93)				
TVR				3.0% (3/100)	3.2% (3/93)				
TLR				1.0% (1/100)	1.1% (1/93)				
Non-TLR				2.0% (2/100)	2.2% (2/93)				
1-Year All death, MI, TVR	9.3% (77/832)	8.4% (68/808)	9.7% (44/455)		7.6% (7/92)	7.0% (7/100)	6.9% (133/1938)****	3.8% (56/1473)****	16.6% (77/465)****
All Death	1.1% (9/832)	1.1% (9/808)	1.3% (6/455)		2.2% (2/92)	5.0% (5/100)	4.9% (94/1938)	2.8% (41/1473)	11.4% (53/465)
Cardiac Death	0.5% (4/832)	0.9% (7/808)	0.7% (3/455)		0.0% (0/92)	1.0% (1/100)	2.6% (51/1938)	1.4% (20/1473)	6.7% (31/465)

Non-cardiac Death	0.6% (5/832)	0.2% (2/808)	0.7% (3/455)		2.2% (2/92)	4.0% (4/100)	1.8% (34/1938)	1.3% (19/1473)	3.2% (15/465)
MI	5.4% (45/832)**	5.0% (40/808)**	5.9% (27/455)**		3.3% (3/92)***	2.0% (2/100)	2.9% (56/1938)	1.4% (20/1473)	7.7% (36/465)
Q-Wave MI	0.2% (2/832)	0.2% (2/808)	0.4% (2/455)		0.0% (0/92)	0.0% (0/100)	0.2% (3/1938)	0.1% (2/1473)	0.2% (1/465)
Non-Q-Wave MI	5.2% (43/832)	4.7% (38/808)	5.5% (25/455)		3.3% (3/92)	2.0% (2/100)	2.8% (54/1938)	1.3% (19/1473)	7.5% (35/465)
TVR	3.8% (32/832)	3.6% (29/808)	5.3% (24/455)		3.3% (3/92)	1.0% (1/100)	2.4% (46/1938)	1.8% (26/1473)	4.3% (20/465)
TLR	2.6% (22/832)	1.7% (14/808)	4.4% (20/455)		1.1% (1/92)	1.0% (1/100)	1.5% (30/1938)	1.2% (17/1473)	2.8% (13/465)
Non-TLR	1.8% (15/832)	2.2% (18/808)	1.8% (8/455)		2.2% (2/92)	1.0% (1/100)	1.2% (23/1938)	0.8% (12/1473)	2.4% (11/465)
15-Month All death, MI, TVR							8.7% (166/1915)****	5.4% (79/1461)****	19.2% (87/454)****
All Death							6.1% (117/1915)	4.2% (61/1461)	12.3% (56/454)
Cardiac Death							3.2% (62/1915)	2.0% (29/1461)	7.3% (33/454)
Non-cardiac Death							2.2% (43/1915)	1.8% (27/1461)	3.5% (16/454)
MI							3.5% (67/1915)	1.8% (26/1461)	9.0% (41/454)
Q-Wave MI							0.2% (3/1915)	0.1% (2/1461)	0.2% (1/454)
Non-Q-Wave MI							3.4% (65/1915)	1.7% (25/1461)	8.8% (40/454)
TVR							3.2% (62/1915)	2.6% (38/1461)	5.3% (24/454)
TLR							2.2% (43/1915)	1.8% (27/1461)	3.5% (16/454)
Non-TLR							1.5% (29/1915)	1.1% (16/1461)	2.9% (13/454)
2-Year All death, MI, TVR	12.8% (105/823)	11.7% (93/797)	14.7% (66/450)		8.7% (8/92)				
3-Year All death, MI, TVR	15.5% (127/819)	14.6% (114/783)	17.5% (78/445)		9.8% (9/92)				
4 -Year All death, MI, TVR	19.2% (156/811)	18.8% (148/787)	21.4% (96/448)		9.8% (9/92)				
5-Year All death, MI, TVR	22.6% (182/807)	22.4% (175/781)	26.7% (119/446)		10.5% (9/86)				
All Death	6.9% (56/807)	7.4% (58/781)	10.3% (46/446)		7.0% (6/86)				
Cardiac Death	3.5% (28/807)	4.2% (33/781)	4.3% (19/446)		1.2% (1/86)				
Non-cardiac Death	3.5% (28/807)	3.2% (25/781)	6.1% (27/446)		5.8% (5/86)				
MI	10.2% (82/807)**	9.0% (70/781)**	11.2% (50/446)**		3.5% (3/86)***				
Q-Wave MI	0.4% (3/807)	0.5% (4/781)	0.7% (3/446)		0.0% (0/86)				
In-Hospital ARC Stent Thrombosis									
Definite or Probable	0.2% (2/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
Definite	0.2% (2/846)	0.0% (0/838)	0.9% (4/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	<0.1% (1/2009)	0.0% (0/1487)	0.2% (1/522)
Probable	0.0% (0/846)	0.0% (0/838)	0.0% (0/466)	0.0% (0/100)	0.0% (0/94)	0.0% (0/100)	0.0% (0/2009)	0.0% (0/1487)	0.0% (0/522)
30-Day ARC Stent Thrombosis									

Definite or Probable	0.4% (3/846)	0.6% (5/833)	1.1% (5/466)	0.0% (0/100)	0.0% (0/93)	0.0% (0/100)	0.2% (4/1995)	0.0% (0/1487)	0.8% (4/508)
Definite	0.2% (2/846)	0.2% (2/833)	1.1% (5/466)	0.0% (0/100)	0.0% (0/93)	0.0% (0/100)	0.1% (1/1995)	0.0% (0/1487)	0.2% (1/508)
Probable	0.1% (1/846)	0.4% (3/833)	0.0% (0/466)	0.0% (0/100)	0.0% (0/93)	0.0% (0/100)	0.2% (3/1995)	0.0% (0/1487)	0.6% (3/508)
9 month ARC Stent Thrombosis									
Definite or Probable				0.0% (0/100)	0.0% (0/92)				
Definite				0.0% (0/100)	0.0% (0/92)				
Probable				0.0% (0/100)	0.0% (0/92)				
1-Year ARC Stent Thrombosis									
Definite or Probable	0.4% (3/832)	0.6% (5/808)	1.1% (5/455)		0.0% (0/91)	0.0% (0/100)	0.4% (8/1938)	0.1% (2/1473)	1.3% (6/465)
Definite	0.2% (2/832)	0.2% (2/808)	1.1% (5/455)		0.0% (0/91)	0.0% (0/100)	0.3% (5/1938)	0.1% (2/1473)	0.6% (3/465)
Probable	0.1% (1/832)	0.4% (3/808)	0.0% (0/455)		0.0% (0/91)	0.0% (0/100)	0.2% (3/1938)	0.0% (0/1473)	0.6% (3/465)
15-Month ARC Stent Thrombosis									
Definite or Probable							0.4% (8/1915)	0.1% (2/1461)	1.3% (6/454)
Definite							0.3% (5/1915)	0.1% (2/1461)	0.7% (3/454)
Probable							0.2% (3/1915)	0.0% (0/1461)	0.7% (3/454)
2-Year ARC Stent Thrombosis									
Definite or Probable	0.4% (3/823)	0.8% (6/797)	1.1% (5/450)		0.0% (0/92)				
3-Year ARC Stent Thrombosis									
Definite or Probable	0.5% (4/819)	0.8% (6/783)	1.1% (5/445)		0.0% (0/92)				
4-Year ARC Stent Thrombosis									
Definite or Probable	0.6% (5/811)	0.9% (7/787)	1.1% (5/448)		0.0% (0/92)				
5-Year ARC Stent Thrombosis									
Definite or Probable	0.7% (6/807)	0.9% (7/781)	1.1% (5/446)		0.0% (0/80)				

[1] DES Control

Numbers are % (count/sample size).

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2- 5 year clinical outcomes are based on the safety population only including patients who received a study stent.

**The MI rates are based on the EVOLVE II MI definition. The definition for MI was as follows:

- Peri-procedural MI:
  - i) Development of new pathological Q-waves or
  - ii) Elevation of CK-MB levels >3x ULN, or if CK-MB is not performed total CK must be >2x ULN, or if Troponin was only available enzyme, it must be >3x ULN. There must also be no evidence of pre-procedure biomarker elevations, or one of the following must be true: ≥50% increase in cardiac biomarker result, or evidence that cardiac biomarker values were decreasing prior to suspected MI or
  - iii) Autopsy evidence of acute MI
- Spontaneous MI definition: Detection of rise and/or fall of CK-MB or Troponin with at least one value above 99th percentile of ULN, together with evidence of myocardial ischemia and at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, development of new pathological Q-waves, imaging evidence of new loss of myocardium or new regional wall abnormality.

***MI rates are based on the EVOLVE Definition. The definition for MI was as follows:

- -: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK-MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1× >ULN and the baseline level must have been <ULN.
- Peri-procedural Non-Q-wave MI: Elevation of CK levels >3x ULN without the presence of new Q-waves, If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >3x ULN and the baseline level must have been <ULN. There must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
- Spontaneous Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1x >ULN and the baseline level must have been <ULN.
- Spontaneous Non-Q-wave MI: De novo elevation of CK levels >2x ULN, without presence of new Q waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >2x ULN and the baseline level must have been <ULN and there must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

**** MI is defined according to the 3rd Universal Definition

Spontaneous MI:

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Percutaneous Coronary Intervention-Related Myocardial Infarction:

Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn value (>5 x 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling.

AND

One of the following:

(i) Symptoms suggestion of myocardial ischemia

(ii) New ischemic ECG changes

(iii) Angiographic findings consistent with a procedural complication

(iv) Imaging demonstration of a new loss of viable myocardial or new regional wall motion abnormality are required

Coronary Artery Bypass Grafting-Related Myocardial Infarction:

Coronary artery bypass graft (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL).

AND

One of the following:

(i) New pathological Q waves or new LBBB

(ii) Angiographic documented new graft or new native coronary artery occlusion

(iii) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Myocardial Infarction resulting in death when biomarker values are unavailable:

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac marker values would be increased.

Stent thrombosis- Related Myocardial Infarction:

MI associated with stent thrombosis when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

The EVOLVE Short DAPT Study used the 3rd Universal Definition of MI*:

Spontaneous MI:

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

- Identification of an intracoronary thrombus by angiography or autopsy

Percutaneous Coronary Intervention-Related Myocardial Infarction

Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn value (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

AND

One of the following:

- Symptoms suggestive of myocardial ischemia
- New ischemic ECG changes
- Angiographic findings consistent with a procedural complication
- Imaging demonstrating new loss of viable myocardial or new regional wall motion abnormality are required.

Coronary Artery Bypass Grafting-Related Myocardial Infarction

Coronary artery bypass graft (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL).

AND

One of the following:

- New pathological Q waves or new LBBB
- Angiographically documented new graft or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac marker values would be increased.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

*Thygesen K, Alpert JS, Jaffe AS et al. Journal of the American College of Cardiology 2012;60:1581-1598.

**** MACE defined as Cardiac Death, MI, TVR in EVOLVE Short DAPT Study

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

9.2 Potential Adverse Events

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
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation, ventricular tachycardia and heart block
- Cardiogenic shock/pulmonary edema
- Death
- Embolization (air, tissue or thrombotic material or material from device(s) used in the procedure); including stent embolization and migration
- Heart failure
- Hemorrhage, which may require transfusion; including bleeding and hematoma
- Hypotension/hypertension
- Infection, local or systemic; including fever and pyrogen reaction
- Myocardial ischemia or infarction
- Pain, chest or access site
- Pericardial effusion or cardiac tamponade
- Renal insufficiency or failure
- Respiratory failure
- Restenosis or aneurysm of stented segment
- Stent deformation, collapse, or fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Vessel trauma requiring surgical repair or reintervention; including coronary, femoral or radial artery spasm, dissection; occlusion, perforation, rupture, or pseudoaneurysm

Zortress™, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day. Outside the U.S., Zortress is sold under the brand name, Certican™, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor™ for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses listed above. The amount of drug that circulates in the bloodstream following implantation of a SYNERGY™ Stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day, see Section 7.2, Pharmacokinetics).

- Abdominal pain
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin

- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of 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)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Vomiting

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

10 CLINICAL STUDIES

10.1 EVOLVE Trial

Primary Objective: The primary objective of the EVOLVE Clinical Trial was to assess the safety and performance of the SYNERGY Everolimus-Eluting Coronary Stent System for the treatment of subjects with a *de novo* atherosclerotic lesion of up to 28 mm in length (by visual estimate) in a native coronary artery 2.25 mm to 3.5 mm in diameter (by visual estimate) compared to PROMUS Element™.

Design: EVOLVE is a prospective, single arm, randomized, multicenter, single blind non-inferiority study. Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of

ischemia or silent ischemia and a left ventricular ejection fraction (LVEF) ≥30%. Patients with stable angina, unstable angina, or silent ischemia were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. The primary clinical endpoint was the 30-day TLF rate defined as a composite of cardiac death or MI related to the target vessel or TLR. The primary endpoint was the 30-day TLF rate defined as a composite of cardiac death or MI related to the target vessel, or TLR. The primary angiographic endpoint was in-stent late loss as measured by QCA at 6 months. A total of 291 patients were enrolled at 29 sites in Europe and Asia-Pacific region (Australia and New Zealand). The protocol mandated antiplatelet therapy compliance in accordance with the 2007 ACC/AHA/SCAI Guidelines for PCI.[10]

The study is now complete including follow-up through 5 years.

Follow-up included a clinical assessment at 30 days, 6, 9 and 12 months, and 2,3,4 and 5 years post index procedure and QCA and IVUS measurements at 6 months. Results are presented in Table 10.1.1.

Demographics: The average patient age was 64.89±11.03 years. Approximately 70% of patients were male, and 17% of patients had medically treated diabetes.

Baseline lesion characteristics: By QCA, mean reference vessel diameter (RVD) was 2.60±0.45 mm. Mean lesion length was 13.41±6.29 mm. Diameter stenosis was 73.95 ± 10.37%, and over 56.0% of treated lesions were type B2/C.

[10] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions.

30-Day and 5 year Clinical Outcomes

Table 10.1.1. EVOLVE SYNERGY™ Arm Clinical Results

Parameter	**SYNERGY (N=94*) ITT population**	
Primary clinical endpoint (30 day TLF)	1.1% (1/92)	
Primary angiographic endpoint (6 month in-stent late loss (mm))	0.10±0.25	
Clinical endpoints**	**30 day (ITT population) (N=94)***	**5 year (Safety population) (N=92)***
All death, MI, TVR	1.1% (1/93)	10.5% (9/86)
All death or MI	1.1% (1/93)	7.0% (6/86)
All death	0.0% (0/93)	7.0% (6/86)
Cardiac death	0.0% (0/93)	1.2% (1/86)
Non-cardiac death	0.0% (0/93)	5.8% (5/86)
MI***	1.1% (1/93)	3.5% (3/86)
Q-wave MI	0.0% (0/93)	0.0% (0/86)
Non–Q-wave MI	1.1% (1/93)	3.5% (3/86)
TVR, overall	0.0% (0/93)	3.5% (3/86)
TLR, overall	0.0% (0/93)	1.2% (1/86)
Non-TLR TVR, overall	0.0% (0/93)	2.3% (2/86)
Cardiac death or MI	1.1% (1/93)	4.8% (4/84)
TLF	1.1% (1/93)	6.0% (5/84)
TVF	1.1% (1/93)	8.3% (7/84)
ARC ST (definite/probable)	0.0% (0/93)	0.0% (0/80)
Peri-procedural endpoints	**SYNERGY (N=94)* ITT population**	

Clinical procedural success	98.9% (92/93)
Quantitative coronary angiography	
Pre-procedure	
Lesion length (mm)	13.41±6.29
Reference vessel diameter (mm)	2.60±0.45
MLD, in-lesion (mm)	0.68±0.30
Diameter stenosis (%)	73.95±10.37
Acute gain, in-stent (mm)	1.83±0.39
Acute gain, in-segment (mm)	1.46±0.44
Post Procedure and 6 month	
MLD, in-stent (mm)	
Post-procedure	2.51±0.37
6 months	2.41±0.42
MLD, in-segment (mm)	
Post-procedure	2.14±0.41
6 months	2.06±0.45
Diameter stenosis, in-stent (%)	
Post-procedure	3.23±9.62
6 months	6.59±9.90
Diameter stenosis, in-segment (%)	
Post-procedure	18.06±8.46
6 months	20.33±10.96
Intravascular ultrasound	
Incomplete stent apposition	
Post-procedure	0.0% (0/78)
6 months	4.2% (3/71)
Vessel area (mm^2)	
Post-procedure	14.06±4.05
6 months	14.51±4.48
Stent area (mm^2)	
Post-procedure	7.17±1.96
6 months	7.03±2.10
Lumen area (mm^2)	
Post-procedure	7.17±1.96
6 months	6.86±2.11

Vessel volume (mm^3)	
Post-procedure	341.87±149.61
6 months	344.73±153.08
Stent volume (mm^3)	
Post-procedure	175.19±77.73
6 months	169.91±75.85
Lumen volume (mm^3)	
Post-procedure	175.19±77.73
6 months	164.22±75.86
In-stent net volume obstruction (%)	
Post-procedure	0.00±0.00
6 months	2.68±4.60

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2 - 5 year clinical outcomes are based on the safety population only including patients who received a study stent.
Numbers are presented as % (count/sample size) or mean ± standard deviation (n).
MLD=minimum lumen diameter.

**Data presented are for full dose SYNERGY Stent.

*** MI rates based on EVOLVE MI Definition:

- Peri-procedural Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1×>ULN and the baseline level must have been <ULN.
- Peri-procedural Non-Q-wave MI: Elevation of CK levels >3x ULN, without the presence of new Q-waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >3x ULN and the baseline level must have been <ULN and there must also be any one of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
- Spontaneous Q-wave MI: Development of new pathological Q-waves in 2 or more leads lasting ≥0.04 seconds with post procedure CK MB levels elevated above normal. If the only enzyme available is Troponin, it must be 1 x >ULN and the baseline level must have been <ULN.
- Spontaneous Non-Q-wave MI: De novo elevation of CK levels >2x ULN, without presence of new Q waves. If CK-MB is performed, must be positive, or if Troponin was only available enzyme, it must be >2x ULN and the baseline level must have been <ULN and there must also be anyone of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality it must be >2x ULN and the baseline level must have been <ULN and there must also be anyone of the following: ECG changes indicative of new ischemia (new ST-T changes or LBBB), imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

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

10.2 EVOLVE II Randomized Controlled Trial (RCT)

Primary Objective: The primary objective of the EVOLVE II RCT was 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 atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[11] Patients

could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was the rate of target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion (TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death, at 12 months post-index procedure. The EVOLVE II RCT was designed to test the hypothesis that the rate of 12 month TLF in patients treated with the SYNERGY Stent is non-inferior to the rate of 12 month TLF in patients treated with the PROMUS Element Plus Stent control.

In the EVOLVE II RCT, MI was defined as follows:

- Peri-procedural MI:
  i) Development of new pathological Q-waves or
  ii) Elevation of CK-MB levels >3x ULN, or if CK-MB is not performed total CK must be >2x ULN, or if Troponin was only available enzyme, it must be >3x ULN. There must also be no evidence of pre-procedure biomarker elevations, or one of the following must be true: ≥50% increase in cardiac biomarker result, or evidence that cardiac biomarker values were decreasing prior to suspected MI or
  iii) Autopsy evidence of acute MI.
- Spontaneous MI definition: Detection of rise and/or fall of CK-MB or Troponin with at least one value above 99th percentile of ULN, together with evidence of myocardial ischemia and at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, development of new pathological Q-waves, imaging evidence of new loss of myocardium or new regional wall abnormality.

A total of 1,684 patients (846 SYNERGY Stent and 838 PROMUS Element Plus Stent) were randomized and enrolled at 125 sites in the Asia-Pacific region, Europe, Japan, Canada and the United States. 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.

Follow-up included clinical assessments at 30 days, 6, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12 month follow-up, the study population was reduced to a pre-specified cohort (Safety Population), which consists of all patients who received a study stent (SYNERGY Stent or PROMUS Element Plus Stent). The study is now complete including follow-up through 5 years.

Results are presented in Tables 10.2.1 to 10.2.9.

Demographics: Patients were well-matched for baseline demographics. Average age was 63.48±10.44 and 63.92±10.50 in the SYNERGY and PROMUS Element Plus Stent groups, respectively. Approximately 70.6% of patients in the SYNERGY Stent group and 72.7% of patients in the PROMUS Element Plus Stent group were male, and 31.1% of patients in the SYNERGY group and 30.8% in the PROMUS Element Plus Stent group had medically treated diabetes. More than a third of patients in each treatment group had unstable angina and more than a quarter had MI diagnosed before the index procedure.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.62±0.49 mm and 2.63±0.50 mm for the SYNERGY and PROMUS Element Plus, respectively. Average lesion length was 14.09±7.50 mm and 13.67±7.00 mm for the SYNERGY and PROMUS Element Plus Stent groups, respectively. In both groups, diameter stenosis was approximately 66%. More than 20% of patients in each treatment group had multiple lesions treated (≥2 lesion), and over 75% of treated lesions were type B2/C complex lesions.

[11] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

Table 10.2.1. EVOLVE II RCT 12 Month and 5-Year Clinical Results.

	12-Month (Intent-to-Treat population)		5-Year (Safety population)	
	SYNERGY (N=846)*	**PROMUS Element Plus[1] (N=838)***	**SYNERGY (N=845)***	**PROMUS Element Plus[1] (N=829)***
EFFICACY				
TVR, Overall	3.8% (32/832)	3.6% (29/808)	11.9% (96/807)	11.1% (87/781)
TLR, Overall	2.6% (22/832)	1.7% (14/808)	6.7% (54/807)	5.2% (41/781)
TLR, PCI	2.0% (17/832)	1.7% (14/808)	6.1% (49/807)	4.9% (38/781)
TLR, CABG	0.6% (5/832)	0.0% (0/808)	1.0% (8/807)	0.4% (3/781)
Non-TLR, Overall	1.8% (15/832)	2.2% (18/808)	6.7% (54/807)	7.7% (60/781)

Non-TLR, PCI	1.4% (12/832)	1.9% (15/808)	6.2% (50/807)	6.8% (53/781)
Non-TLR, CABG	0.4% (3/832)	0.4% (3/808)	0.6% (5/807)	1.2% (9/781)
SAFETY				
Total Death	1.1% (9/832)	1.1% (9/808)	6.9% (56/807)	7.4% (58/781)
Cardiac Death or MI	5.6% (47/832)	5.6% (45/808)	12.5% (101/807)	12.3% (96/781)
Cardiac Death	0.5% (4/832)	0.9% (7/808)	3.5% (28/807)	4.2% (33/781)
MI	5.4% (45/832)	5.0% (40/808)	10.2% (82/807)	9.0% (70/781)
Q-wave MI	0.2% (2/832)	0.2% (2/808)	0.4% (3/807)	0.5% (4/781)
Non−Q-wave MI	5.2% (43/832)	4.7% (38/808)	9.9% (80/807)	8.5% (66/781)
ARC Stent Thrombosis	0.6% (5/832)	0.7% (6/808)	2.5% (20/807)	3.2% (25/781)
Definite or Probable	0.4% (3/832)	0.6% (5/808)	0.7% (6/807)	0.9% (7/781)
Definite	0.2% (2/832)	0.2% (2/808)	0.6% (5/807)	0.5% (4/781)
Probable	0.1% (1/832)	0.4% (3/808)	0.1% (1/807)	0.4% (3/781)

[1] DES Control
* 1 year outcomes are based on Intent-to-treat (ITT) population. 2-5 year clinical outcomes are based on the safety population only including patients who received a study stent.
Numbers are % (count/sample size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Primary Endpoint (12 Month TLF): The primary endpoint was met. The SYNERGY Stent was shown to be non-inferior to the PROMUS Element Plus Stent with regard to the rate of 12 month TLF (Table 10.2.2).

Table 10.2.2 EVOLVE II RCT Primary Endpoint 12 month TLF

Per Protocol Patients	**SYNERGY (N=843)**	**PROMUS Element Plus[1] (N=829)**	**Difference**	**One-sided 97.5% Farrington-Manning Upper Confidence Bound**	**Non-Inferiority Margin**	***P* value[2]**
	6.4% (53/823)	6.4% (51/796)	0.0% [-2.4%, 2.4%]	2.51%	4.4%	0.0003
Intent-to-Treat Patients	**SYNERGY (N=846)**	**PROMUS Element Plus[1] (N=838)**	**Difference**	**One-sided 97.5% Farrington-Manning Upper Confidence Bound**	**Non-Inferiority Margin**	***P* value[2]**
	6.7% (55/826)	6.5% (52/804)	0.2% [-2.2%, 2.6%]	2.68%	4.4%	0.0005

[1] DES Control
[2] *P* values are one-sided from the Farrington-Manning test and are based on the standard normal distribution.
12 Month TLF: the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 10.2.3 EVOLVE II Post-Procedure Angiographic Results by Lesion

Angiographic Outcomes	**SYNERGY™ (N=1059 Lesions, N=846 Subjects)**	**PROMUS Element ™ Plus[1] (N=1043 Lesions, N=838 Subjects)**
MLD (mm), In-stent	2.44 ± 0.44	2.46 ± 0.44
MLD (mm), Analysis Segment	2.10 ± 0.47	2.10 ± 0.47
Acute Gain (mm), In-stent	1.55 ± 0.45	1.57 ± 0.45
Acute Gain, Analysis Segment (mm)	1.22 ± 0.48	1.21 ± 0.47
% DS, In-stent	7.19 ± 9.16	6.55 ± 9.71
% DS, Analysis Segment	20.60 ± 8.41	20.93 ± 9.13

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

Table 10.2.4 EVOLVE II ARC Definite and Probable Stent Thrombosis

Intent-to-Treat and Safety Patients	**SYNERGY (N=846)[1]**	**PROMUS Element Plus[4] (N=838) [1]**
ARC Definite & Probable Stent Thrombosis[2]	0.7% (6/807)	0.9% (7/781)
Acute ST (≤24 hrs)	0.2% (2/846)	0.0% (0/838)
Subacute ST (>24 hrs and ≤30 days)	0.1% (1/846)	0.6% (5/834)
Late ST (>30 days and ≤12 months)[3]	0.0% (0/843)	0.0% (0/826)
Very Late ST (>365 days and ≤ 1855)	0.4% (3/826)	0.2% (2/802)

[1] 1-year outcomes are based on ITT. 1-5 and 2-5 year clinical outcomes are based on the Safety population only including patients who received a study stent.
[2] To be included in the calculation of 5-year stent thrombosis (ST) rate, a patient either had to have a CEC confirmed safety event during the 5 years or had to be CEC event-free during
the 5 years with last follow-up on or after the 5-year visit window.
[3] To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31 - 365 days inclusive) or
had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).
[4] DES Control
Academic Research Consortium (ARC) stent thrombosis is defined as follows.[12]

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases: Any unexplained death within the first 30 days following stent implantation.

Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

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

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

[12] Cutlip DE, Windecker S, Mehran R, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation.2007;115:2344-2351.

10.2.5 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, Event Rate 1.5 SE, All Patients (N=1684)

	Event Rate	Event Free	Log-Rank *P* value
SYNERGY	6.7%	93.3%	0.8314
PROMUS Element Plus	6.2%	93.8%	

Results in Males and Females

EVOLVE II was not designed or powered to study safety or effectiveness of the SYNERGY Stent versus the PROMUS Element Plus Stent in gender-specific subgroups, so these analyses are considered hypothesis-generating.

In the EVOLVE II ITT population, of the 846 patients randomized to SYNERGY, 597 patients were male (70.6%) and 249 patients were female (29.4%). The proportions in the PROMUS Element Plus group were similar (72.7% males, 27.3% females).

In the United States, an estimated 15,400,000 adults age 20 and older (7.9% of men and 5.1% of women) suffer from coronary artery disease (CAD).[13] However, it is estimated that only 33% of annual PCIs are performed in women. In PCI clinical trials, women represent only 25 – 35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology,[14,15] which may lead to under-diagnosis and under-referral of female patients with CAD. Once diagnosed and treated, poorer revascularization outcomes have been reported in women due to smaller coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men.

In patients treated with the SYNERGY Stent, the 12 month rate of TLF was 7.0% in males and 5.7% in females. In patients treated with the PROMUS Element Plus Stent, the 12 month rate of TLF was 5.6% in males and 8.7% in females (Table 10.2.6). 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.

[13] Go AS, Mozaffarian D, Roger VL, et al. Executive Summary: Heart Disease and Stroke Statistics—2014 Update: A Report From the American Heart Association. Circulation. 2014;129(3):399-410.

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

[15] Lundberg G, King S. Coronary Revascularization in Women. Clin Cardiol. 2012;35(3):156-159.

Table 10.2.6 EVOLVE II RCT Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=1684)

12 month TLF	SYNERGY Stent (N=846)	PROMUS Element Plus Stent (N=838)	Difference
Female (N=478)	**(N=249)**	**(N=229)**	
	5.7% (14/244)	8.7% (19/218)	-3.0% [-7.7%, 1.8%]
Male	**(N=597)**	**(N=609)**	

(N=1206)	7.0% (41/582)	5.6% (33/586)	1.4% [-1.4%, 4.2%]

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

Table 10.2.7 shows EVOLVE II RCT 12 month and 5-Year clinical results for SYNERGY Stent male and female patients. Outcomes were similar in male and female patients.

Table 10.2.7 EVOLVE II 12 Month and 5-Year Clinical Endpoints by Gender SYNERGY Stent Male and Female Patients

	12-Month (ITT population)		**5-Year (Safety population)**	
	SYNERGY Stent Female Subjects (N=249)*	**SYNERGY Stent Male Subjects (N=597)***	**SYNERGY Stent Female Subjects (N=249)***	**SYNERGY Stent Male Subjects (N=596)***
Efficacy				
TVR, Overall	3.3% (8/246)	4.1% (24/586)	11.6% (28/241)	12.0% (68/566)
TLR, Overall	2.4% (6/246)	2.7% (16/586)	7.1% (17/241)	6.5% (37/566)
TLR, PCI	2.0% (5/246)	2.0% (12/586)	6.2% (15/241)	6.0% (34/566)
TLR, CABG	0.4% (1/246)	0.7% (4/586)	1.2% (3/241)	0.9% (5/566)
Non-TLR, Overall	1.6% (4/246)	1.9% (11/586)	6.6% (16/241)	6.7% (38/566)
Non-TLR, PCI	1.6% (4/246)	1.4% (8/586)	6.2% (15/241)	6.2% (35/566)
Non-TLR, CABG	0.0% (0/246)	0.5% (3/586)	0.8% (2/241)	0.5% (3/566)
TLF	5.7% (14/246)	7.0% (41/586)	15.4% (37/241)	14.0% (79/566)
Safety				
Total Death	1.2% (3/246)	1.0% (6/586)	9.1% (22/241)	6.0% (34/566)
Cardiac Death or MI	5.3% (13/246)	5.8% (34/586)	14.1% (34/241)	11.8% (67/566)
Cardiac Death	0.8% (2/246)	0.3% (2/586)	3.3% (8/241)	3.5% (20/566)
MI	4.5% (11/246)	5.8% (34/586)	11.2% (27/241)	9.7% (55/566)
Q-wave MI	0.0% (0/246)	0.3% (2/586)	0.4% (1/241)	0.4% (2/566)
Non-Q-wave MI	4.5% (11/246)	5.5% (32/586)	10.8% (26/241)	9.5% (54/566)
ARC Stent Thrombosis	1.2% (3/246)	0.3% (2/586)	2.9% (7/241)	2.3% (13/566)
Definite or Probable	0.8% (2/246)	0.2% (1/586)	1.2% (3/241)	0.5% (3/566)
Definite	0.4% (1/246)	0.2% (1/586)	0.8% (2/241)	0.5% (3/566)
Probable	0.4% (1/246)	0.0% (0/586)	0.4% (1/241)	0.0% (0/566)

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2- 5 year clinical outcomes are based on the safety population only including patients who received a study stent.
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (count/sample size).
Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass grafting; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization.

Tables 10.2.8 and 10.2.9 show the cumulative rate of TLF through 12 months for males and females in both the SYNERGY and PROMUS Element Plus Stent, respectively. This post hoc analysis shows a difference in treatment and gender groups. 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.

Table 10.2.8 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Male Patients (N=1206)

	Event Rate	Event Free
SYNERGY™ (N=597)	7.0%	93.0%
PROMUS Element™ Plus (N=609)	5.5%	94.5%

Table 10.2.9 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Female Patients (N=478)

	Event Rate	Event Free
SYNERGY (N=249)	6.0%	94.0%
PROMUS Element Plus (N=229)	8.4%	91.6%

10.3 EVOLVE II Diabetic (DM) Sub-study

Primary Objective: The primary objective of the EVOLVE II DM sub-study was to evaluate the safety and effectiveness of the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of diabetic patients with atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Eligible patients were to have diabetes (treated with oral agent, insulin or another injectable agent), be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[16] Patients could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was the rate of target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion
(TLR), MI (Q-wave and non–Q-wave) related to the target vessel, or cardiac death, at 12 months post-index procedure. The EVOLVE II DM sub-study was designed to test the hypothesis that the rate of 12 month TLF in patients treated with the SYNERGY Stent was less than a prespecified performance goal (PG) of 14.5%. The PG was based on data from patients with diabetes in the PLATINUM,
SPIRIT IV, COMPARE, and EVOLVE trials adjusted for the expected increase in the 12-month non-Q-wave MI rate using CK-MB >3x upper limit of normal (ULN) instead of the historical definition with total CK >2x ULN.

The EVOLVE II DM sub-study pooled: 1) diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patients with 2) diabetes subjects enrolled in the non-randomized Diabetes single-arm study (203 patients from 48 sites in Asia-Pacific region, Europe, Canada and the United States), following completion of EVOLVE II RCT enrollment. A total of 460 intention-to-treat patients were evaluable for the 12 month primary endpoint.

Follow-up included clinical assessments at 30 days, 6, 12 and 18 months, and 2, 3, 4 and 5 years post index procedure. After the 12 month follow-up, the study population was reduced to a prespecified cohort (Safety Population), which consists of all patients who received a study stent.

The study is now complete including follow-up through 5 years.

Results are presented in Tables 10.3.1 and 10.3.2. The primary endpoint of the DM sub-study was met as the one-sided upper 97.5% confidence bound for 1 year TLF was below the pre-specified performance goal of 14.5% (Table 10.3.2). A poolability analysis found that the TLF rate in diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT (263 patients) was higher than the TLF rate in the diabetic patients enrolled in the

non-randomized Diabetes single-arm study (203 subjects) due to differences in the geographic pattern of enrollment and in biomarker collection between the two cohorts. The differences in the 1 year TLF rate were driven primarily by non-Q-wave MI and particularly peri-procedural non-Q-wave MI. When non-Q-wave MI or peri-procedural non-Q-wave MI were excluded from the calculation of TLF, the TLF rate was not statistically different between the two cohorts (Table 10.3.3). Sensitivity analysis showed that the primary endpoint would still have been met even if the TLF rate in the single arm cohort was not lower than in the diabetic patients randomized to the SYNERGY arm of the EVOLVE II RCT.

Demographics: Average age of patients in the DM sub-study was 65% and 70% of the patients were male. The majority of the patients were treated with an oral agent (83.3%, 388/466)) while 37.3% (174/466) of patients were treated with insulin and 0.6% (0/466) were treated with an injectable agent other than insulin. More than a third of patients had unstable angina and more than a quarter had MI diagnosed before the index procedure.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.56±0.50 and average lesion length was 14.10±7.49. Baseline diameter stenosis was 65.47±11.70. Twenty percent of patients had 2 lesions treated and 74.9% of treated lesions were type B2/C complex lesions.

[16] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651

Table 10.3.1 EVOLVE II DM Sub-study 12 Month and 5 -Year Clinical Results

	12-Month (ITT population)	5-Year (Safety population)
	SYNERGY (N=466)*	SYNERGY (N=463)*
EFFICACY		
TVR, Overall	5.3% (24/455)	14.8% (66/446)
TLR, Overall	4.4% (20/455)	9.0% (40/446)
TLR, PCI	3.5% (16/455)	8.1% (36/446)
TLR, CABG	0.9% (4/455)	1.6% (7/446)
Non-TLR, Overall	1.8% (8/455)	9.0% (40/446)
Non-TLR, PCI	1.3% (6/455)	8.3% (37/446)
Non-TLR, CABG	0.4% (2/455)	1.1% (5/446)
SAFETY		
Total Death	1.3% (6/455)	10.3% (46/446)
Cardiac Death or MI	6.2% (28/455)	14.1% (63/446)
Cardiac Death	0.7% (3/455)	4.3% (19/446)
MI	5.9% (27/455)	11.2% (50/446)
Q-wave MI	0.4% (2/455)	0.7% (3/446)
Non−Q-wave MI	5.5% (25/455)	10.8% (48/446)
ARC Stent Thrombosis	1.5% (7/455)	3.1% (14/446)
Definite or Probable	1.1% (5/455)	1.1% (5/446)
Definite	1.1% (5/455)	1.1% (5/446)
Probable	0.0% (0/455)	0.0% (0/446)

* 1 year outcomes are based on Intent-to-treat (ITT) population. 2-5 year clinical outcomes are based on the safety population only including patients who received a study stent.
Numbers are % (count/sample size).
This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; DES=drug-eluting stent; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Table 10.3.2 EVOLVE II DM Sub-study Primary Endpoint

Primary Endpoint: 12 month TLF	Overall Diabetic Subjects	One-sided Clopper-Pearson 97.5% Upper Confidence Bound	Performance Goal	One Sided *P* value[1]
Intent-to-Treat Subjects	**(N=466)** 7.5% (34/451)	10.4%	14.5%	<0.0001
Per Protocol Subjects	**(N=463)** 7.4% (33/448)	10.2%	14.5%	<0.0001

Numbers are % (counts/sample size)
[1] One-group Clopper-Pearson test
Abbreviations: 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)

Table 10.3.3 EVOLVE II DM Sub-study TLF with and without Peri-procedure NQMI

Event	Diabetic Subjects from RCT (N=263 Subjects)	Subjects from Diabetic Sub-study (N=203 Subjects)	*P* value
TLF	10.2% (26/256)	4.0% (8/199)	0.0135
TLF exluding non-Q-wave MI	6.6% (17/256)	3.0% (6/199)	0.0799
TLF exluding Peri-Procedure non-Q-wave MI	6.6% (17/256)	3.5% (7/199)	0.1393

10.4 EVOLVE II Quantitative Coronary Angiography (QCA) Trial

Primary Objective: The primary objective of the EVOLVE II QCA Trial was to evaluate the clinical, angiographic, and IVUS outcomes of the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of atherosclerotic lesions of up to 34 mm in length (by visual estimate) in native coronary arteries of ≥2.25 mm to ≤4.00 mm in diameter (by visual estimate).

Design: EVOLVE II QCA is a prospective, single-arm, multi-center, observational trial with the SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System. Eligible patients were to be ≥18 years of age and have symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia. Patients with stable angina, unstable angina, silent ischemia or NSTEMI (but not STEMI) were eligible for inclusion in the trial. Lesions were to be coverable by a single study stent and to have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. Additionally, at least one of the following was to be present: lesion stenosis ≥70%, abnormal fractional flow reserve, abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. The protocol mandated antiplatelet therapy compliance in accordance with ACC/AHA/SCAI/ESC Guidelines for PCI.[17] Patients could have up to 3 target lesions in 2 epicardial vessels treated. The primary endpoint was in-stent late loss at 9 months post-procedure as measured by quantitative coronary angiography (QCA). No formal statistical testing was performed for the primary endpoint

in this single arm observational trial. All patients were required to undergo 9 month angiography and IVUS assessments.

For the 9 month in-stent late loss, the performance goal was based on historical PLATINUM QCA and PROMUS™ arm of RESOLUTE all-comers results.

No adjustments were made for multiple comparisons. MI was defined as described in the EVOLVE II (see Section 10.2).

A total of 100 patients were enrolled at 12 sites. Of the 100 patients included in the intent-to-treat analysis set, all were evaluable for the 9 month primary endpoint, 95 underwent angiography at 9 months post procedure, and 90 underwent IVUS at 9 months post procedure.

Follow-up included clinical assessments at 30 days, 9 months and 12 months post index procedure, and angiographic and IVUS assessments at 9 months post procedure. Angiographic assessments were performed for the area of the vessel within the stent margins (in-stent) and the areas immediately 5 mm proximal and distal from the stent margins (analysis segment). The study is now complete.

Results are presented in Tables 10.4.1 to 10.4.4.

Demographics: Average age was 64.49±10.21 years. 80% of patients were male, and 17% of patients had medically treated diabetes.

Baseline lesion characteristics: Reference vessel diameter was 2.66 ± 0.46 mm with baseline lesion length 14.38 ± 7.49 mm. Percent diameter stenosis was 67.54±9.59% and 74.1% of treated lesions were type B2/C.

[17] Levine GN, Bates ER, Blankenship JC, et al. Circulation 2011; 124:e574-e651.

Table 10.4.1 EVOLVE II QCA 9 Month Clinical Results, Intent-to-Treat, All Patients

	SYNERGY Stent (N=100)
EFFICACY	
TVR, Overall	3.0% (3/100)
TLR, Overall	1.0% (1/100)
TLR, PCI	1.0% (1/100)
TLR, CABG	0.0% (0/100)
Non-TLR, Overall	2.0% (2/100)
Non-TLR, PCI	2.0% (2/100)
Non-TLR, CABG	0.0% (0/100)
SAFETY	
Total Death	0.0% (0/100)
Cardiac Death or MI	5.0% (5/100)
Cardiac Death	0.0% (0/100)
MI	5.0% (5/100)
Q-wave MI	0.0% (0/100)
Non−Q-wave MI	5.0% (5/100)
ARC Stent Thrombosis	0.0% (0/100)
Definite or Probable	0.0% (0/100)
Definite	0.0% (0/100)
Probable	0.0% (0/100)
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (count/sample size).	

Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization; TVR=target vessel revascularization.

Primary Endpoint (9 month In-stent Late Loss by QCA): In-stent late loss of 0.23±0.34 mm was significantly less than the performance goal of 0.40 mm (*P*<0.0001) at 9 months. No adjustments to *P* values were made for multiple comparisons.

Table 10.4.2 EVOLVE II QCA Primary Endpoint: 9 Month In-stent Late Loss

Per-protocol and Intent to treat	SYNERGY Stent (N=100)	[95% CI]	One-sided 95% upper confidence bound	Performance Goal	*P* value[1]
9 Month In-Stent Late Loss, mm	0.23±0.34	[0.16, 0.29]	0.30	0.40	<.0001

[1] A one-group t-test is used.

Table 10.4.3 EVOLVE II QCA Angiographic and IVUS Results

	SYNERGY (N=100)
Angiographic Outcomes[1]	
MLD (mm), In-stent	
Post-Procedure	2.51±0.44
9 Month	2.29±0.46
MLD (mm), Analysis Segment	
Post-Procedure	2.16±0.45
9 Month	2.06±0.46
Acute Gain (mm), In-stent	1.65±0.41
Acute Gain, Analysis Segment (mm)	1.30±0.43
% DS, In-stent	
Post-Procedure	6.83±8.57
9 Month	13.54±12.49
% DS, Analysis Segment	
Post-Procedure	20.02±7.77
9 Month	22.39±11.27
Late Loss, In-stent (mm) (9 months)	0.22±0.33
Late Loss, Analysis Segment (mm) (9 months)	0.10±0.30
Binary Restenosis	
In-stent Restenosis	1.8% (2/110)
Analysis segment restenosis	3.6% (4/110)
IVUS Outcomes	
Neointimal Volume (mm^3) (9 months)	9.67±14.57

% In-stent Net Volume Obstruction (9 months)	5.19±5.67
Incomplete Apposition	
Late (9 months)	6.5% (6/92)
Late Acquired	3.4% (3/88)
[1] Includes all patients with paired lesion data Numbers are % (count/sample size) or mean±SD (n).	

Results in Males and Females:

EVOLVE II QCA was not designed or powered to study safety or effectiveness of the SYNERGY Stent in gender-specific subgroups, so these analyses were performed *post hoc* and are considered hypothesis-generating.

In the EVOLVE II QCA ITT population, of the 100 patients enrolled, 80 patients were male (80.0%) and 20 patients were female (20.0%). In patients treated with the SYNERGY Stent, the 9 month rate of TLF was 5% in males and 10% in females (Table 10.3.4). Table 10.3.4 also shows the EVOLVE II QCA primary endpoint for males and females. Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 10.4.4 EVOLVE II QCA 9 Month Results by Gender, Intent-to-Treat, SYNERGY Male and Female Patients (N=100)

	SYNERGY Stent Male Patients (N=80)	**SYNERGY Stent Female Patients (N=20)**
9 Month TLF	5.0% (4/80)	10.0% (2/20)
9 Month In-stent Late Loss	0.22±0.34	0.26±0.33
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (count/sample size). TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 270 days post-procedure out of the population that have been followed for at least 24 days or who have experienced a TLF up to 270 days post-procedure.		

10.5 EVOLVE 48 Trial

Primary Objective: The primary objective of the EVOLVE 48 trial is to evaluate the safety and effectiveness of the SYNERGY™ 48 mm Coronary Stent System for the treatment of subjects with atherosclerotic lesion(s) >34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate).

Design: Subjects were ≥18 years of age with either (1) symptomatic coronary artery disease and stenosis ≥70%, abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure or (2) silent ischemia based abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure. Subjects received the SYNERGY 48 mm stent for treatment of native coronary artery with a reference vessel diameter (RVD) ≥2.5 mm and ≤4.0 mm and lesion length >34 mm and ≤44 mm (both by visual estimate). Target lesion(s) had visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1.

In the EVOLVE 48 trial, MI is defined according to the 3rd Universal Definition

Spontaneous MI:

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Percutaneous Coronary Intervention-Related Myocardial Infarction:

Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn value (>5 x 99th percentile URL) in patients with normal baseline values ($\leq$ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling.

AND

One of the following:

(i) Symptoms suggestion of myocardial ischemia

(ii) New ischemic ECG changes

(iii) Angiographic findings consistent with a procedural complication

(iv) Imaging demonstration of a new loss of viable myocardial or new regional wall motion abnormality are required

Coronary Artery Bypass Grafting-Related Myocardial Infarction:

Coronary artery bypass graft (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values ($\leq$99th percentile URL).

AND

One of the following:

(iv) New pathological Q waves or new LBBB

(v) Angiographic documented new graft or new native coronary artery occlusion

(vi) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Myocardial Infarction resulting in death when biomarker values are unavailable:

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac marker values would be increased.

Stent Thrombosis-Related Myocardial Infarction:

MI associated with stent thrombosis when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

A total of 100 subjects were enrolled in the trial in the US, Europe and New Zealand.

Follow-up includes clinical assessments at 30 days, 6 months, 1 year and 2 years post index procedure. The study is ongoing with follow up through 2 years.

Results through 30 days and 12 months are presented in Tables 10.5.1 through 10.5.3.

Demographics: The mean age was about 65 years, 40% of subjects were female, and 27% of subjects had medically-treated diabetes mellitus.

Baseline lesion characteristics: The angiographically determined mean reference vessel diameter was 2.72±0.44 mm, mean lesion length was 35.34±7.15 mm, minimum lumen diameter was 0.78±0.43 mm, and mean percent diameter stenosis was 71.23±14.98%.

TABLE 10.5.1 EVOLVE 48: 30 Day and 12 Month Clinical Results

	SYNERGY 48 mm (N=100) 30 Day	**SYNERGY 48 mm (N=100) 12 Month**
EFFICACY		
TVR, Overall	0.0% (0/100)	1.0% (1/100)
TLR, Overall	0.0% (0/100)	1.0% (1/100)
TLR, PCI	0.0% (0/100)	1.0% (1/100)
TLR, CABG	0.0% (0/100)	0.0% (0/100)

Non-TLR, Overall	0.0% (0/100)	1.0% (1/100)
Non-TLR, PCI	0.0% (0/100)	1.0% (1/100)
Non-TLR, CABG	0.0% (0/100)	0.0% (0/100)
SAFETY		
Total Death	0.0% (0/100)	5.0% (5/100)
Cardiac Death or MI	0.0% (0/100)	3.0% (3/100)
Cardiac Death	0.0% (0/100)	1.0% (1/100)
MI	0.0% (0/100)	2.0% (2/100)
Q-wave MI	0.0% (0/100)	0.0% (0/100)
Non−Q-wave MI	0.0% (0/100)	2.0% (2/100)
ARC Stent Thrombosis	0.0% (0/100)	0.0% (0/100)
Definite or Probable	0.0% (0/100)	0.0% (0/100)
Definite	0.0% (0/100)	0.0% (0/100)
Probable	0.0% (0/100)	0.0% (0/100)

Primary Endpoint (12 Month TLF): The primary endpoint performance goal was met. The TLF rate of 4.1% was significantly less than the performance goal of 19.5% at 12 months (P<0.0001). See Table 10.5.2.

TABLE 10.5.2 EVOLVE 48 Primary Endpoint 12 Month TLF

EVOLVE 48 mm* (N=100)	[95% CI][a]	95% UCB[b] (one-sided)	Performance Goal	*P* value[c] (one-sided)
4.1% (4/98)	[1.1%, 10.1%]	9.1%	19.5%	<0.0001

Numbers are % (count/sample size)

*The ITT and per-protocol populations are the same

[a]: 95% CI is from two-sided Clopper-Pearson Exact Method

[b]: Clopper-Pearson upper confidence bound

[c]: *P* value is one-sided from the Exact test

Note: Subjects with respective event or sufficient follow up are included in the denominator, two subjects without TLF event and without sufficient follow-up 335 days were excluded from denominator.

TABLE 10.5.3 EVOLVE 48 Post-Procedure QCA Results by Lesion

	SYNERGY 48 mm (N=100)
Angiographic Outcomes	
MLD (mm), In-stent	2.47±0.40
MLD (mm), Analysis Segment	2.18±0.44
Acute Gain (mm), In-stent	1.68±0.51
Acute Gain, Analysis Segment (mm)	1.39±0.52
% DS, In-stent	9.74±7.19

% DS, Analysis Segment	20.83±8.69
Numbers are % (count/sample size) or mean±SD (n).	

Results in Males and Females:

EVOLVE 48 was not designed or powered to study safety or effectiveness of the SYNERGY Stent in gender-specific subgroups, so these analyses were performed *post hoc* and are considered hypothesis-generating.

In the EVOLVE 48 study, of the 100 patients enrolled, 60 patients were male (60.0%) and 40 patients were female (40.0%). Gender based data is available in Table 10.5.4.

TABLE 10.5.4 EVOLVE 48 Primary Endpoint Results by Gender, Male and Female Patients (N=100)

	Male Patients (N=60)	Female Patients (N=40)
12 Month TLF	6.8% (4/59)	0.0% (0/39)
Numbers are % (count/sample size).		

Note: Subjects with respective event or sufficient follow up are included in the denominator, two subjects without TLF event and without sufficient follow-up 335 days were excluded from denominator.

Real World Evidence

The SYNERGY 48 mm stent has been commercialized in Sweden since February 2017, and data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) provides real world evidence on the outcomes in an unselected population. The registry provides extensive data from all 29 centers in Sweden that perform PCI. A 500-patient cohort of patients treated with the SYNERGY 48 mm stent, and no other non-SYNERGY stents, who had follow-up through 1-year was identified. The group was predominately male (78%), had an average age of 69.4 years, and 25% were medically treated diabetics. Outcomes at 1-year included all-cause death (6.8%), myocardial infarction (3.0%), target lesion revascularizations 4.4%and a derived target lesion failure rate of 11.2% (defined as the composite of all deaths, all myocardial infarctions, and all target lesion revascularizations). Stent thrombosis occurred in two SYNERGY 48 mm stents (0.4%). The data from SCAAR demonstrates positive real-world evidence on the SYNERGY 48 mm stent.

10.6 EVOLVE Short DAPT Study

Primary Objective: The primary objective of the EVOLVE Short DAPT Study is to assess the safety of 3-month DAPT in subjects at high risk for bleeding undergoing PCI with the SYNERGY Stent System.

Design: The EVOLVE Short DAPT Study* is a prospective, multi-center, single-arm study in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent. A historical control and a propensity score approach was used to assess the safety of 3-month DAPT in high bleeding risk patients. High bleeding risk subjects were enrolled if they met one or more of the following criteria: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit; need for chronic or lifelong anticoagulation, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); platelet count ≤100,000/μL. Subjects were prescribed dual antiplatelet therapy ($P2Y_{12}$ inhibitor + aspirin) between 0-3 months post-procedure. Aspirin was optional between 0-3 months for subjects on chronic anticoagulation. Subjects were eligible to discontinue $P2Y_{12}$ inhibitor at 3 months if they were compliant with the prescribed dual antiplatelet therapy and were free from events between 0-3 months (stent thrombosis, myocardial infarction, revascularization, or stroke). Subjects that discontinued $P2Y_{12}$ inhibitor at 3-months were prescribed aspirin through the end of study. The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or MI, and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis related to SYNERGY. The control group for the death/MI primary endpoint includes propensity-matched historical sirolimus, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the PROMUS Element Plus Post-Approval Study (PE+PAS), PE-PROVE Study and the DAPT Study. The second co-primary endpoint was ARC definite/probable stent thrombosis related to SYNERGY compared to pre-specified performance goal (1.0%). The pre-specified secondary endpoint is the rate of bleeding, using the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) between 3-15 months post-index procedure in subjects not receiving chronic anticoagulation. The control group for the secondary bleeding endpoint includes propensity-matched historical sirolimus-, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the DAPT Study, excluding subjects on chronic

anticoagulation. A total of 2,009 patients were enrolled at 110 sites in the United States, Europe, Brazil and Japan, of which 1,487 patients were eligible to and discontinued $P2Y_{12}$ inhibitor at 3-months (3-month DAPT group). Patients were followed at 3-, 6-, 12- and 15-months post-index procedure. The study is considered complete with follow-up through 15-months.

Results are presented in Tables 10.6.1 to 10.6.6.

Demographics: In subjects that discontinued $P2Y_{12}$ inhibitor at 3-months (n=1,487), the mean age in the 3-month group was 75.7 years, 34.0% were female, and subjects had a mean BMI of 28.7.

Baseline/Lesion Characteristics: Thirty-six percent subjects that discontinued $P2Y_{12}$ inhibitor at 3-months had diabetes, 26% had unstable angina, 48% stable angina and 9% silent ischemia (STEMI and NSTEMI patients were excluded from enrollment). Prior myocardial infarction, heart failure and atrial fibrillation were present in 23%, 26% and 31% of subjects, respectively. Visually-estimated mean reference vessel diameter was 3.0±0.5 mm, mean lesion length was 17.2±9.5 mm, and mean percent diameter stenosis was 82.6±9.8%.

Table 10.6.1. EVOLVE Short DAPT Study 3-15 months Outcomes in the 3-Month DAPT group

	SYNERGY (N=1487)
TVR, Overall	2.6% (38/1457)
TLR	1.9% (28/1457)
Non-TLR	1.2% (17/1457)
Total Death	4.3% (62/1457)
Death or MI	5.8% (84/1457)
Cardiac Death or MI	3.6% (52/1457)
Cardiac Death	2.1% (30/1457)
Non-Cardiac Death	1.9% (27/1457)
MI	1.9% (27/1457)
Q-wave MI	0.2% (3/1457)
Non−Q-wave MI	1.7% (25/1457)
Stroke	1.4% (21/1457)
BARC 2,3,5 Bleeding	7.1% (103/1457)
BARC 2	4.6% (67/1457)
BARC 3	2.7% (40/1457)
BARC 5	0.2% (3/1457)
ARC Stent Thrombosis; Definite or Probable; Related to SYNERGY	0.2% (3/1457)

Co-Primary Endpoints: The study has 2 powered co-primary endpoints assessed between 3- and 15- months post index procedure: (1) the rate of death from any cause or myocardial infarction (MI), and (2) the rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST), related to the SYNERGY stent. The EVOLVE Short DAPT study was considered a success as both the co-primary endpoints of death/MI and ARC definite/probable ST were met. In high bleeding risk patients, death/MI in the 3-month DAPT group

implanted with the SYNERGY stent was non-inferior to 12-month DAPT historical control. ARC definite/probable ST related to the SYNERGY stent in the 3-month DAPT group treated with the SYNERGY stent was significantly lower than the pre-specified performance goal. Results for the two co-primary endpoints are in Tables 10.6.2 and 10.6.3.

Table 10.6.2: Co-Primary Endpoint: Death/MI between 3-15 months

12-month DAPT[d] N=1948	3-month DAPT N=1487	Difference [95% CI]	One-sided 97.5% UCB[a]	NI Margin	P-value[c]
5.70%	5.58%	-0.12% [-1.87%, 1.63%]	1.63%	2.52%	0.0016

Numbers are % (count/sample size)
a: Z-test upper confidence bound (UCB)
b: Non-inferiority margin
c: *P* value is from one-tailed Z-test and is based on normal approximation to binomial
Subjects with respective event or sufficient follow up were included in the denominator; N=1454 in 3-month DAPT test group and N=1493 in 12-month DAPT control group
d: The control group for the death/MI primary endpoint includes propensity-matched historical sirolimus, zotarolimus- and everolimus-eluting stent-treated subjects at high risk for bleeding obtained from the PROMUS Element Plus Post-Approval Study (PE+PAS), PE-PROVE Study and the DAPT Study.

Table 10.6.3 Co-Primary Endpoint (3-15-month ARC Definite/Probable Stent Thrombosis Related to SYNERGY)

3-month DAPT (N=1487)	[95% CI]	One-sided 97.5% UCB[a]	Performance goal	P-value[b]
0.2% (3/1396)	[0.04%, 0.63%]	0.63%	1.0%	0.0005

Numbers are % (count/sample size)
a: Exact test upper confidence bound (UCB)
b: *P* value is from one-sided exact test for single proportion
Subjects with respective event or sufficient follow up were included in the denominator; N=1397 in 3-month DAPT test group

Secondary Endpoint: The secondary endpoint is the rate of bleeding, using the BARC classification (types 2, 3 and 5) between 3- and 15-months post index procedure in subjects not receiving chronic anticoagulation. The study secondary endpoint was not met; however, residual confounding despite propensity matching and better ascertainment of bleeding events in the EVOLVE Short DAPT Study as compared to the historical control may have contributed to this outcome as shorter duration DAPT is expected to reduce the risk of bleeding. Results for the secondary endpoint are in Table 10.6.4.

Table 10.6.4: Secondary Endpoint: BARC 2/3/5 Bleeding between 3-15 months

12-month DAPT N=1333	3-month DAPT N=1032	Difference [95% CI]	One-sided 97.5% UCB[a]	Superiority Test P-value[b]
4.17%	6.26%	2.10% [-0.10%, 4.29%]	4.29%	0.9820

Numbers are % (count/sample size)
a: Z-test upper confidence bound (UCB)
b: *P* value is from one-tailed Z-test and is based on normal approximation to binomial
Subjects with respective event or sufficient follow up were included in the denominator; N=974 in 3-month DAPT test group and N=947 in 12-month DAPT control group

Results in Males and Females

The EVOLVE Short DAPT Study was not powered to evaluate safety or effectiveness of the SYNERGY Stent in gender-specific subgroups, therefore these analyses are considered hypothesis-generating.

In the EVOLVE Short DAPT Study, of the 1,487 subjects that discontinued P2Y12 inhibitor at 3-months (3-Month DAPT group), 981 patients were male (66%) and 506 patients were female (34%).

In the 3-month DAPT group, the death/MI rate between 3-15 months was 6.1% in males and 5.1% in females. The ARC definite/probable stent thrombosis (related to SYNERGY) rate was 0.3% in males and 0.0% in females. The BARC 2,3,5 bleeding rate was 5.9% in males and 6.0% in females. No statistically significant differences between male and females were observed for the pre-specified primary and secondary endpoints. The overall conclusions of the trial regarding the safety of the SYNERGY Stent with 3-months of DAPT in patients at high risk of bleeding can be generalized to males and females.

Table 10.6.5 EVOLVE Short DAPT Study – Co-Primary and Secondary Endpoints (3-15 months) in the 3-Month DAPT group (n=1487)

	3-Month DAPT Group (N=1487)	
	Male (N=981)	**Female (N=506)**
Death and MI	6.1% (59/966)	5.1% (25/491)
ARC ST (Definite/Probable) related to SYNERGY stent	0.3% (3/966)	0.0% (0/491)
Bleeding (BARC 2/3/5)	5.9% (37/624)	6.0% (23/386)

Table 10.6.6. shows EVOLVE Short DAPT Study clinical results for the 3-Month DAPT group between 3-15 months for male and female patients. Outcomes were similar in male and female patients although the trend suggests fewer ischemic complications in females.

Table 10.6.6 EVOLVE Short DAPT Study Clinical Outcomes by Gender; 3-Month DAPT group (3-15 months)

	3-Month DAPT Group (n=1487)	
	SYNERGY Stent Male Subjects (N=981)	**SYNERGY Stent Female Subjects (N=506)**
TVR, Overall	2.9% (28/966)	2.0% (10/491)
TLR	2.1% (20/966)	1.6% (8/491)
Non-TLR	1.1% (11/966)	1.2% (6/491)
TLF	4.7% (45/966)	3.9% (19/491)
Total Death	4.3% (42/966)	4.1% (20/491)
Death or MI	6.1% (59/966)	5.1% (25/491)
Cardiac Death or MI	3.8% (37/966)	3.1% (15/491)
Cardiac Death	2.1% (20/966)	2.0% (10/491)
Non-Cardiac Death	1.9% (18/966)	1.8% (9/491)
MI	2.0% (19/966)	1.6% (8/491)
Q-wave MI	0.2% (2/966)	0.2% (1/491)
Non-Q-wave MI	1.9% (18/966)	1.4% (7/491)
Stroke	1.2% (12/966)	1.8% (9/491)
BARC 2,3,5 Bleeding	7.0% (68/966)	7.1% (35/491)
BARC 2	5.0% (48/966)	3.9% (19/491)
BARC 3	2.5% (24/966)	3.3% (16/491)
BARC 5	0.1% (1/966)	0.4% (2/491)

ARC Stent Thrombosis	1.2% (12/966)	0.6% (3/491)
Definite or Probable	0.3% (3/966)	0.0% (0/491)
Definite	0.3% (3/966)	0.0% (0/491)
Probable	0.0% (0/966)	0.0% (0/491)

The overall conclusions of the trial regarding the safety of the SYNERGY Stent with 3-months of DAPT in patients at high risk of bleeding can be generalized to males and females.

11 INDIVIDUALIZATION OF TREATMENT

See Section 6.7, Use in Special Populations and Section 6.8, Lesion/Vessel Characteristics.

The risks and benefits should be carefully considered for each patient before use of the SYNERGY™ XD Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged antiplatelet therapy. On the basis of randomized clinical trial protocols, a $P2Y_{12}$ inhibitor should be given for at least 6 months after everolimus-eluting stent (EES) implantation and ideally up to 12 months. Aspirin should be administered concomitantly with the $P2Y_{12}$ inhibitor and then continued indefinitely. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease) in whom antiplatelet therapy would be contraindicated.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure and severe obesity) should be reviewed.

12 PATIENT COUNSELING INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks/benefits issues for this particular patient.
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide (included in the package and available on-line) which includes both product information and a stent implant card.
- An Angioplasty and Stent Education Guide (available on-line or by request) which includes information on coronary artery disease, the implant procedure and frequently asked questions.

13 HOW SUPPLIED

STERILE: This product is sterilized with ethylene oxide gas. It is intended for single use only. Do not resterilize.

The SYNERGY XD Everolimus-Eluting Platinum Chromium Coronary Stent System is sterile, non-pyrogenic in unopened, undamaged packaging.

Do not use if package is opened or damaged.

Do not use if labeling is incomplete or illegible.

HANDLING and STORAGE:

Keep dry and protect from light. Recommended storage at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F).

Store product in outer carton.

DO NOT REMOVE FROM FOIL POUCH UNTIL READY FOR USE.

Do not store devices where they are directly exposed to organic solvents or ionizing radiation.

The foil pouch contains nitrogen gas (N_2) and desiccant as a storage medium.

DISPOSAL INSTRUCTIONS: After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

14 OPERATIONAL INSTRUCTIONS

14.1 Inspection Prior to Use

Check foil pouch for ‘‘Use By’’ date. Do not use the product after the ‘‘Use By’’ date. Carefully inspect the foil pouch before opening. If the integrity of the foil pouch has been compromised prior to the product ‘‘Use By’’ date

(e.g., damage of the package), contact your local Boston Scientific representative for return information. Do not use if any defects are noted.

Note: At any time during use of the SYNERGY XD Monorail™ Stent Delivery System, if the proximal shaft (hypotube) has been bent or kinked, do not continue to use the catheter.

14.2 Materials Required (not included in Stent Delivery System package)

Quantity	Material
1	Appropriate guide catheter (see Table 2.1, SYNERGY XD Stent System Product Description)
2 – 3	20 ml (cc) syringe
1000 u/500 cc	Normal heparinized sterile saline
1	≤0.014 in (0.36 mm) guidewire
1	Hemostatic valve
1	Diluted contrast medium 1:1 with normal heparinized sterile saline
1	Inflation Device
1	Torque Device
1	Pre-deployment dilation catheter
1	Three-way stopcock
1	Appropriate arterial sheath

14.3 Preparation

14.3.1 Packaging Removal

Step **Action**

1. Open the outer box to reveal the foil pouch and carefully inspect the foil pouch for damage.
2. Carefully peel open the foil pouch using aseptic techniques and extract the stent delivery system.
3. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. Do not bend or kink proximal shaft during removal.
4. Remove the product mandrel and stent protector by grasping the catheter just proximal to the stent protector, and with the other hand, grasp the distal end of the stent protector and gently remove.

Note: If unusual resistance is felt during product mandrel and stent protector removal, do not use the product and replace with another.

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5. Examine the device for any damage. If it is suspected that the sterility or performance of the device has been compromised, the device should not be used.

14.3.2 Guidewire Lumen Flush

Step **Action**

1. Flush the stent delivery system guidewire lumen with normal heparinized saline using the flushing needle supplied for the Monorail delivery system at the distal end.
2. Verify that the stent is positioned between the proximal and distal balloon markers. Check for bends, kinks and other damage. Do not use if any defects are noted.

Note: Avoid manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.

Note: Use caution while flushing guidewire lumen with flushing needle to avoid damage to catheter tip.

14.3.3 Balloon Preparation

Step	Action
1.	Stent contact with any fluid is not recommended, as there is a possibility of initiating drug release. However, if it is absolutely necessary to flush the stent with saline, contact time should be limited (1 minute maximum).
2.	Prepare inflation device/syringe with diluted contrast medium.
3.	Attach inflation device/syringe to stopcock; attach to inflation port. Do not bend the proximal shaft when connecting to inflation device/syringe.
4.	With tip down, orient stent delivery system vertically.
5.	Open stopcock to stent delivery system; pull negative for 15 seconds; release to neutral for contrast fill.
6.	Close stopcock to stent delivery system; purge inflation device/syringe of all air.
7.	Repeat steps 4 through 6 until all air is expelled. If bubbles persist, do not use product.
8.	If a syringe was used, attach a prepared inflation device to stopcock.
9.	Open stopcock to stent delivery system.
10.	Leave on neutral.

14.3.4 Delivery Procedure

Step	Action
1.	Obtain vascular access according to standard PTCA practice. Select a guide catheter that provides adequate support and coaxial alignment with the coronary ostium to deliver interventional equipment.
2.	Pre-dilate the lesion/vessel with appropriate diameter balloon.
3.	Maintain neutral pressure on inflation device attached to stent delivery system.
4.	Backload stent delivery system onto proximal portion of guidewire while maintaining guidewire position across target lesion.
5.	Fully open hemostatic valve to allow for easy passage of the stent and prevent damage to the stent.
6.	Carefully advance the stent delivery system into the hub of the guide catheter. Be sure to keep the proximal shaft straight. Ensure guide catheter stability before advancing the stent delivery system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guide catheter, do not force passage. Resistance may indicate a problem, and use of excessive force may result in stent damage or stent dislodgment from the balloon. Maintain guidewire placement across the lesion, and remove the stent delivery system and guide catheter as a single unit.

7.	Advance the stent delivery system over the guidewire to target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque balloon markers as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also Precautions – Section 6.15, Stent Delivery System Removal). The inside edges of the marker bands indicate both the stent edges and balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

Note: If unusual resistance is felt at any time during lesion access before stent implantation, the stent delivery system and the guide catheter should be removed as a single unit. (See also Precautions – Section 6.15, Stent Delivery System Removal). Once the stent delivery system has been removed do not re-use.

8.	Sufficiently tighten the hemostatic valve. The stent is now ready to be deployed.

14.3.5 Deployment Procedure

Step	Action
1.	Inflate the delivery system expanding the stent to a minimum pressure of 11 atm (1117 kPa). Higher pressure may be necessary to optimize stent apposition to the arterial wall. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter of about 1.1 times the reference vessel diameter (see Table 14.1). Balloon pressure must not exceed rated burst pressure of 18 atm (1827 kPa) for the 2.25 mm – 2.75 mm diameter stents and 16 atm (1620 kPa) for the 3.00 mm – 5.00 mm diameter stent sizes (see Table 14.1).

2. Maintain inflation pressure for 15 seconds– 30 seconds for full expansion of the stent.
3. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
4. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through angiography or intravascular ultrasound (IVUS).
5. If stent sizing/apposition requires optimization, re-advance the stent delivery system balloon, or another high-pressure, balloon catheter of the appropriate size, to the stented area using standard angioplasty techniques.
6. Inflate the balloon to the desired pressure while observing under fluoroscopy (refer to product labeling and/or Table 14.1 for balloon compliance chart). Deflate the balloon. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds, for balloon deflation. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
7. If more than one SYNERGY™ XD Stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second SYNERGY XD Stent should be positioned inside of the deployed stent prior to expansion.
8. Reconfirm stent position and angiographic result. Repeat inflations until optimal stent deployment is achieved.

14.3.6 Removal Procedure

Step Action

1. Deflate balloon by pulling negative pressure on inflation device until balloon is fully deflated. Ensure balloon is fully deflated before delivery system withdrawal. Larger and longer balloons will take more time to deflate than smaller and shorter balloons. Allow adequate time, at least 30 seconds. Before withdrawing the stent delivery system visually confirm complete balloon deflation under fluoroscopy.
2. Fully open hemostatic valve.
3. While maintaining guidewire position and negative pressure on inflation device, withdraw delivery system.
4. Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.

Post-Deployment Dilation of Stented Segments

Precaution: Do not dilate the stent beyond the limits tabulated below.

Nominal Stent Diameter (ID)	Dilation Limits (ID)*
2.25 mm, 2.50 mm, 2.75 mm	3.50 mm
3.00 mm, 3.50 mm	4.25 mm
4.00 mm, 4.50 mm, 5.00 mm	5.75 mm

*Max Stent Inner Diameter

All efforts should be taken to assure that the stent is not under-dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger post dilation balloon catheter may be used to expand the stent. The stent may be expanded using a low profile and high pressure balloon catheter. If this is required, the stented segment should be re-crossed carefully with a

prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

Note: In line with Section 6.16, Post-Procedure: Care must be exercised when crossing a newly deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating.

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5. Complete angiographic confirmation, remove devices, and close vascular access site according to standard practice.

14.4 In Vitro Information

Table 14.1 Typical SYNERGY XD Stent System Compliance

Pressure atm (kPa)	Stent Inner Diameters (mm)							
	2.25 mm	2.50 mm	2.75 mm	3.00 mm	3.50 mm	4.00 mm	4.50 mm	5.00 mm
6 (607)						3.55		
7 (710)				2.72	3.19	3.68		
8 (814)	2.09			2.81	3.31	3.81	4.11	4.62
9 (910)	2.14	2.40	2.63	2.89	3.40	3.90	4.24	4.73
10 (1014)	2.19	2.46	2.70	2.96	3.47	3.99	4.35	4.85
11 Nominal (1117)	2.25	2.52	2.76	3.02	3.55	4.06	4.46	4.95
12 (1213)	2.29	2.57	2.82	3.06	3.60	4.12	4.54	5.03
13 (1317)	2.32	2.61	2.87	3.11	3.66	4.18	4.61	5.11
14 (1420)	2.36	2.65	2.90	3.15	3.70	4.22	4.68	5.17
15 (1517)	2.38	2.68	2.94	3.18	3.74	4.27	4.73	5.22
16*(1620)	2.41	2.71	2.97	3.21	3.78	4.32	4.78	5.28
17 (1724)	2.43	2.74	3.00	3.25	3.82	4.37	4.83	5.34
18* (1827)	2.46	2.77	3.03	3.29	3.88	4.44	4.89	5.39
19 (1924)	2.48	2.80	3.06	3.34	3.94	4.52	4.96	5.45
20 (2027)		2.83	3.10	3.39	4.01		5.04	5.50

* RATED BURST PRESSURE. DO NOT EXCEED.
Note: The Stent I.D. values listed are actual average stent inner diameters at the specific balloon inflation pressures obtained during in vitro testing at 37°C. Balloon pressure must not exceed rated burst pressure of 18 atm (1827 kPa) for the 2.25 mm – 2.75 mm diameter stents and 16 atm (1620 kPa) for the 3.00 mm – 5.00 mm diameter stent sizes.

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