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SYNERGY MEGATRON™

MONORAIL™

Everolimus-Eluting Platinum Chromium Coronary Stent System

TABLE OF CONTENTS

1 REUSE WARNING 1

2 DEVICE DESCRIPTION 1

Table 2.1 SYNERGY MEGATRON Stent System Product Description 2

2.1 User Information 2

2.2 Non-Pyrogenic 2

2.3 Device Component Description 2

2.4 Drug Component Description 2

2.4.1 Everolimus 2

Figure 2.1 The Chemical Structure of Everolimus 2

2.4.2 Polymer Carrier 2

Figure 2.2 The Chemical Structure of PLGA 2

2.4.3 Product Matrix and Everolimus Content 2

Table 2.2 SYNERGY MEGATRON Stent System Product Matrix and Everolimus Content 2

2.5 Operating Principle 2

3 INTENDED USE/INDICATIONS FOR USE 3

4 CONTRAINDICATIONS 3

5 WARNINGS 3

6 PRECAUTIONS 3

6.1 General Precautions 3

6.2 Pre- and Post-Procedure Antiplatelet Regimen 3

6.2.1 Oral Antiplatelet Therapy 3

6.3 Longitudinal Stent Deformation 3

6.4 Use of Multiple Stents 3

6.5 Brachytherapy 3

6.6 Use in Conjunction with Other Procedures 3

6.7 Use in Special Populations 3

6.7.1 Pregnancy 3

6.7.2 Lactation 3

6.7.3 Gender 3

6.7.4 Ethnicity 3

6.7.5 Pediatric Use 3

6.7.6 Geriatric Use 3

6.8 Lesion/Vessel Characteristics 4

6.9 Drug Interactions 4

6.10 Magnetic Resonance Imaging (MRI) Safety Information 4

6.11 Stent System Handling 4

6.12 Stent Placement 4

6.13 Stent Delivery System Removal 4

6.14 Post-Procedure 4

7 DRUG INFORMATION 4

7.1 Mechanism of Action 4

7.2 Pharmacokinetics 4

Table 7.1 Whole Blood Everolimus Pharmacokinetic Parameters (Mean ± SD) for SYNERGY (Groups with Three or More Patients) Following SYNERGY Stent Implantation. 5

7.3 Drug Interactions 5

7.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity 5

7.5 Pregnancy 5

7.6 Lactation 5

8 OVERVIEW OF CLINICAL STUDIES 5

8.1 EVOLVE Clinical Trial 5

8.2 EVOLVE II Clinical Trial 5

8.2.1 Randomized Controlled Trial (RCT) 5

8.2.2 Pharmacokinetics (PK) Sub-study 6

8.2.3 Diabetic (DM) Sub-study 6

8.3 EVOLVE II Quantitative Coronary Angiography (QCA) Trial 6

8.4 EVOLVE Short DAPT Study 6

Table 8.1 Comparison of EVOLVE Clinical Studies 6

9 ADVERSE EVENTS 7

9.1 Observed Adverse Events 7

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 From Post-Procedure to 15-month Follow-up 7

9.2 Potential Adverse Events 10

10 CLINICAL STUDIES 10

10.1 EVOLVE Trial 10

Table 10.1.1. EVOLVE SYNERGY Arm Clinical Results 10

10.2 EVOLVE II Randomized Controlled Trial (RCT) 11

Table 10.2.1. EVOLVE II RCT 12-Month and 5-Year Clinical Results 11

Table 10.2.2 EVOLVE II RCT Primary Endpoint 12-Month TLF 12

Table 10.2.3 EVOLVE II Post-Procedure Angiographic Results by Lesion 12

Table 10.2.4 EVOLVE II 5-Year ARC Definite and Probable Stent Thrombosis 12

Table 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) 12

Table 10.2.6 EVOLVE II RCT Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=1684) 12

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

Table 10.2.8 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Male Patients (N=1206) 13

Table 10.2.9 EVOLVE II RCT Cumulative Rate of Target Lesion Failure to 12 Months, Intent-to-Treat, All Female Patients (N=478) 13

10.3 EVOLVE II Diabetic (DM) Sub-study 13

Table 10.3.1 EVOLVE II DM Sub-study 12-Month and 5-Year Clinical Results 13

Table 10.3.2 EVOLVE II DM Sub-study Primary Endpoint 13

Table 10.3.3 EVOLVE II DM Sub-study TLF with and without Peri-procedure NQMI 14

10.4 EVOLVE II Quantitative Coronary Angiography (QCA) Trial 14

Table 10.4.1 EVOLVE II QCA 9 Month Clinical Results, Intent-to-Treat, All Patients 14

Table 10.4.2 EVOLVE II QCA Primary Endpoint: 9-Month In-stent Late Loss 14

Table 10.4.3 EVOLVE II QCA Angiographic and IVUS Results 14

Table 10.4.4 EVOLVE II QCA 9-Month Results by Gender, Intent-to-Treat, SYNERGY Male and Female Patients (N=100) 15

10.5 EVOLVE Short DAPT Study 15

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

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

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

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

Table 10.5.5 EVOLVE Short DAPT Study – Co-Primary and Secondary Endpoints (3-15 months) in the 3-Month DAPT group (N=1487) 16

Table 10.5.6 EVOLVE Short DAPT Study Clinical Outcomes by Gender; 3-Month DAPT group (3-15 months) 16

11 INDIVIDUALIZATION OF TREATMENT 16

12 PATIENT COUNSELING INFORMATION 16

Expected Lifetime 16

13 HOW SUPPLIED 16

14 OPERATIONAL INSTRUCTIONS 16

14.1 Inspection Prior to Use 16

14.2 Additional Items for Safe Use (not included in Stent Delivery System package) 17

14.3 Preparation 17

14.3.1 Packaging Removal 17

14.3.2 Guidewire Lumen Flush 17

14.3.3 Balloon Preparation 17

14.3.4 Delivery Procedure 17

14.3.5 Deployment Procedure 17

14.3.6 Removal Procedure 17

14.4 Compatibility Information for Two Devices in a Guide Catheter 18

14.5 Post-Procedure 18

14.6 In Vitro Information 18

Table 14.1 Typical SYNERGY MEGATRON Stent System Compliance 18

15 WARRANTY 18

16 SYMBOL DEFINITIONS 18

℞ 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) are sterile. The external surface of the sterile barrier pouch, as well as the product carton, should not be considered sterile.

1 REUSE WARNING

Carefully read all instructions prior to use. Observe all warnings and precautions noted throughout these instructions. Failure to do so may result in complications.

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.

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.

2 DEVICE DESCRIPTION

The SYNERGY MEGATRON Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY MEGATRON Stent System) is a device/drug combination product consisting of a drug/polymer-coated balloon expandable stent, pre-mounted on a Monorail 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 MEGATRON Stent System are described in Table 2.1. SYNERGY MEGATRON Stent System Product Description:

BSC (MB IFU Template 8.2677 x 11.6929 A4, 92310060J), eIFU, MB, SYNERGY MEGATRON, en, 51466419-01A

Table 2.1 SYNERGY MEGATRON Stent System Product Description

	SYNERGY MEGATRON Monorail Stent Delivery System
Drug Coated Stent	
Available Stent Lengths (mm)	8, 12, 16, 20, 24, 28, 32
Available Stent Diameters (mm)	3.50, 4.00, 4.50, 5.00
Stent Material	Platinum Chromium Alloy (PtCr) (PtCr alloy components: platinum, chromium, iron, nickel, and molybdenum)
Stent Strut Thickness	0.089 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 237 µg on the longest stent.
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)
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: 16 atm (1620 kPa)
Catheter Shaft Outer Diameter	Proximal: 2.1F (0.70 mm) Distal: 3.50 mm: • 8 mm – 20 mm: 2.6F (0.89 mm) • 24 mm – 32 mm: 2.7F (0.92 mm) 4.00 mm - 5.00 mm: • 8 mm - 32 mm: 2.7F (0.92 mm)
Guide Catheter Compatibility (ID)	3.50 - 4.00 mm: ≥5F (0.056 inches/1.42 mm) 4.50 - 5.00 mm: ≥6F (0.070 inches/1.78 mm)

2.1 User Information

Only physicians who are experienced in percutaneous coronary interventions should perform implantation of the stent.

2.2 Non-Pyrogenic

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

2.3 Device Component Description

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

The SYNERGY MEGATRON Stent System is available in a single stent model which covers 3.50 mm, 4.00 mm, 4.50 mm and 5.00 mm diameters.

Contents for (1) SYNERGY MEGATRON Monorail Stent System

• One (1) SYNERGY MEGATRON Monorail Stent System

2.4 Drug Component Description

The stent component of the SYNERGY MEGATRON 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** for descriptions of drug and polymer, respectively.

2.4.1 Everolimus

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

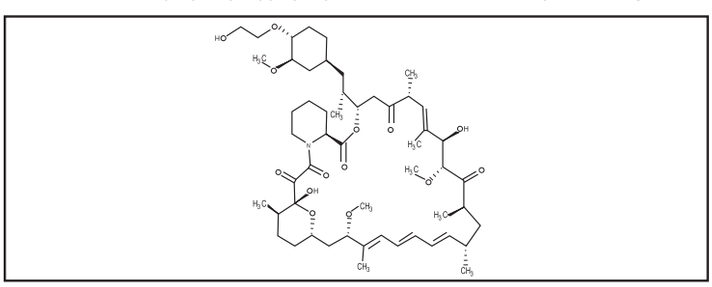

Figure 2.1 The Chemical Structure of Everolimus

2.4.2 Polymer Carrier

The SYNERGY MEGATRON 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.

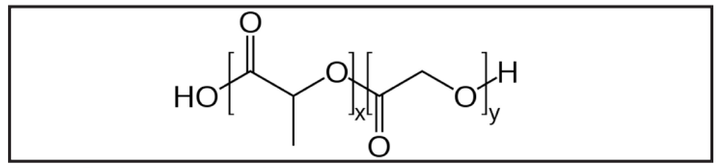

Figure 2.2 The Chemical Structure of PLGA

2.4.3 Product Matrix and Everolimus Content

Table 2.2 SYNERGY MEGATRON Stent System Product Matrix and Everolimus Content

Product Code	Nominal Expanded Stent Inner Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
H7493942808350	3.50	8	61.5
H7493942808400	4.00	8	61.5
H7493942808450	4.50	8	61.5
H7493942808500	5.00	8	61.5
H7493942812350	3.50	12	87.9
H7493942812400	4.00	12	87.9
H7493942812450	4.50	12	87.9
H7493942812500	5.00	12	87.9
H7493942816350	3.50	16	123.1
H7493942816400	4.00	16	123.1
H7493942816450	4.50	16	123.1
H7493942816500	5.00	16	123.1
H7493942820350	3.50	20	149.5
H7493942820400	4.00	20	149.5
H7493942820450	4.50	20	149.5
H7493942820500	5.00	20	149.5
H7493942824350	3.50	24	175.8
H7493942824400	4.00	24	175.8
H7493942824450	4.50	24	175.8
H7493942824500	5.00	24	175.8
H7493942828350	3.50	28	211.0
H7493942828400	4.00	28	211.0
H7493942828450	4.50	28	211.0
H7493942828500	5.00	28	211.0
H7493942832350	3.50	32	237.4
H7493942832400	4.00	32	237.4
H7493942832450	4.50	32	237.4
H7493942832500	5.00	32	237.4

2.5 Operating Principle

The vascular access site is prepared according to standard practice and the lesion is then prepared, for example with a pre-dilation catheter.

The SYNERGY MEGATRON device is prepared and the proximal end of the guidewire is inserted through the distal tip. The distal section of the SYNERGY MEGATRON device is dual lumen and coaxial - the inner lumen is the guidewire lumen for the delivery system and the outer lumen is used for inflation and deflation of the balloon. The delivery system is advanced over the guidewire and through a guide catheter to the target lesion. The location of the balloon and stent is monitored using fluoroscopy via the radiopaque stent component and marker bands.

When the target lesion is reached, the balloon is expanded using an inflation device to deploy the drug-coated stent. The inflation device is attached to the manifold port via a stopcock. Diluted contrast media passes through the manifold and single-lumen hypotube to the distal section of the delivery system. Once the stent is deployed, the delivery system with deflated balloon is retrieved back through the guide catheter and over the guidewire. Stent apposition is assessed using intravascular imaging and post-dilation is completed if required.

The abluminal stent polymer coating elutes the Everolimus drug for the purpose of limiting restenosis which could occur as the tissue responds to the newly placed stent. After the drug is eluted and the polymer is absorbed, the stent scaffold remains, providing long-term mechanical support to the vessel.

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3 INTENDED USE/INDICATIONS FOR USE

The SYNERGY MEGATRON 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 ≥3.50 mm to ≤5.00 mm in diameter in lesions ≤28 mm in length.

4 CONTRAINDICATIONS

Use of the SYNERGY MEGATRON 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 are experienced in percutaneous coronary interventions should perform implantation of the stent.
- Stent placement should only be performed at medical facilities where emergency open-heart surgery is readily available.
- Prior to angioplasty, carefully examine all equipment to be used during the procedure including the dilatation catheter to verify proper function.
- 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 complete 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 drug eluting stents 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 drug eluting stents 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.
- Used devices may pose a biohazard risk and must be handled and disposed of properly.

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

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 post-procedure antiplatelet therapy than was recommended 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 MEGATRON 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 intravascular imaging 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 IFU (see sections 14.3.4 Delivery Procedure, 14.3.5 Deployment Procedure, 14.3.6 Removal Procedure).

[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.

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Black (K) ΔE ≤5.0

6.8 Lesion/Vessel Characteristics

The safety and effectiveness of the SYNERGY MEGATRON 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 <3.50 or >5.00 mm.
- Patients with coronary artery lesions longer than 28 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.

6.10 Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that the SYNERGY MEGATRON Stent is MR Conditional for single and overlapped conditions up to 66 mm in 1.5 T and 3.0 T MR systems. A patient with this device can be safely scanned in a Magnetic Resonance system meeting the following conditions. Failure to follow these conditions may result in injury to the patient. If information about a specific parameter is not included, there are no conditions associated with that parameter.

- Static magnetic field of 3.0 Tesla and 1.5 Tesla only
- Maximum spatial gradient magnetic field of 2000 gauss/cm (20.0 T/m) for 1.5 T systems and 1060 gauss/cm (10.6 T/m) for 3.0 T systems
- Maximum Magnetic Resonance system reported, whole body averaged specific absorption rate (SAR) of ≤2 W/kg (Normal Operating Mode)
- Scanner Type: Horizonal, Cylindrical bore
- RF Excitation: CP (Circular Polarization) 90
- RF Transmit/ Receive Coil Type: Integrated Whole-Body Transmit/Receive Coil
- Scan Duration: Up to 15 minutes of continuous RF (a sequence or back-to-back series/scan without breaks), followed by 5 minutes of cooling.

Under the scan conditions defined above, the SYNERGY MEGATRON Stent is expected to produce a maximum temperature rise of 5.7°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 10 mm from the SYNERGY MEGATRON stent when imaged with a gradient echo pulse sequence and a 3 T MRI system as specified in ASTM F2119-01.

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 artifact does obscure the device lumen. Image artifact was minimized using the spin echo sequence vs. 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

MR Conditional

6.11 Stent System 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, Reuse Warning)
- The premounted SYNERGY MEGATRON 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.
- Excessive handling can cause catheter damage such as delivery system kinking, shaft rupture or separation which may necessitate additional procedures. Do not bend or kink the device during removal from the packaging.
- 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.
- Improper handling before or during deployment, or interaction with ancillary intravascular devices or subsequent intravascular procedures may lead to stent deformation, collapse, fracture, or device separation. Stent deformation, collapse, fracture, or separation may potentially result in embolization/migration, vessel injury, restenosis, or stent thrombosis. Use caution to avoid stent damage during and after implantation.
- 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 MEGATRON Stent is expanded or damaged, do not use the product and contact your local Boston Scientific Representative for return information.

6.12 Stent Placement

Preparation

- Prepare the balloon prior to stent deployment as directed. Do not pre-inflate the balloon prior to stent deployment. Use the balloon purging technique described in Section 14.3.3, Balloon Preparation.
- The target lesion 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 6.13 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 delivery balloon may occur.

Placement

- Do not expand the stent if it is not properly positioned in the vessel (see Section 6.13, Stent Delivery System Removal).
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on product label (see Section 14.6, In Vitro Information, Table 14.1, Typical SYNERGY MEGATRON Stent System Compliance). Use of pressures higher than specified on the product label may result in a ruptured balloon or shaft. This may result in potential intimal damage, dissection or vessel rupture.
- The stent inner diameter should approximate 1.1 times the reference diameter of the vessel, taking into consideration vessel taper.
- Stent placement may potentially compromise neighboring side branch patency.
- Stent implantation may cause dissection of the vessel distal and/or proximal to the stented portion which may lead to acute vessel closure requiring additional intervention (e.g. further dilation, placement of additional stents, or coronary artery bypass grafting (CABG) surgery).
- When treating multiple lesions in the same vessel, the distal lesion should be stented first, followed by stenting of the more proximal lesion(s). Stenting in this order avoids the requirement to cross the proximal stent when placing the distal stent and reduces the chances of stent dislodgment or deformation.

6.13 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 proximal 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 delivery balloon, and/or damage to the delivery system.

6.14 Post-Procedure

- Care must be exercised when crossing a recently 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 6.10, 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.

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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
$t_{1/2\ term}$ [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

Possible interactions of everolimus from SYNERGY MEGATRON Stent System with concomitantly administered medications have not been formally investigated. Drug interactions of systemic therapeutic levels of everolimus with possible concomitant medications are outlined in the labeling for finished pharmaceuticals containing everolimus, such as Afinitor or Zortress. Given that the amount of everolimus loaded onto each SYNERGY MEGATRON Stent is 6-84 times lower than the daily dose used in transplant and cancer patients and systemic everolimus levels are below the limit of detection in preclinical studies after two days, drug interactions are unlikely to be detectable. This is reinforced since systemic levels of everolimus were found to be close to or below limit of quantitation of 0.2 ng/ml beyond 48 hours post-stent placement in clinical trials. See Section 7.2, Pharmacokinetics.

7.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The SYNERGY MEGATRON Stent was assessed to be non-genotoxic in both the in vitro and in vivo genotoxicity tests. Although no carcinogenicity or reproductive toxicity testing was conducted on SYNERGY MEGATRON Stent, prior testing completed on PROMUS (XIENCE V) as well as toxicity literature on bare metal stent and polymer coating support no carcinogenicity or reproductive toxicity concerns from SYNERGY MEGATRON Stent in patients. PROMUS (XIENCE V) and SYNERGY MEGATRON use the same drug (everolimus) and release profile.

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.

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 MEGATRON 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 MEGATRON 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 MEGATRON Stent and continued for one year post-implantation. The SYNERGY MEGATRON Stent should be used in pregnant women only if the potential benefits justify the potential risks.

Safety of the SYNERGY MEGATRON 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 MEGATRON 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 MEGATRON 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 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. A summary of the EVOLVE, EVOLVE II RCT, PK, DM, and QCA, 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.

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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 through 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 EVOLVE Clinical Studies

	EVOLVE	EVOLVE II				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 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	2009 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				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: 2.25, 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; DM=diabetes mellitus; IVUS=intravascular ultrasound; MI=myocardial infarction; PK=pharmacokinetics; QCA=quantitative coronary angiography; RCT=randomized controlled trial; TLF=target lesion failure.

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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 From Post-Procedure to 15-month Follow-up.

	EVOLVE II RCT**		EVOLVE II DM**	EVOLVE II QCA**	EVOLVE***	EVOLVE SHORT DAPT****		
	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)			

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	EVOLVE II RCT**		EVOLVE II DM**	EVOLVE II QCA**	EVOLVE***	EVOLVE SHORT DAPT****		
	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)
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)			

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[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.

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 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 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.

***MI rates are based on the EVOLVE Definition. The 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.

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

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.

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9.2 Potential Adverse Events

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

- Allergic or adverse reaction (including medications, anesthesia, contrast, or device materials)
- Angina
- Arrhythmias, including ventricular fibrillation, ventricular tachycardia and heart block
- Bleeding including hemorrhage or hematoma (possibly requiring transfusion or additional intervention)
- Cardiac failure leading to low cardiac output (cardiogenic shock) or pulmonary edema
- Death
- Emboli (including air, tissue, thrombus, or device materials)
- Fever and pyrogen reaction
- Heart failure
- Hypotension/hypertension
- Infection, local or systemic
- Myocardial infarction
- Pain or inflammation
- Pericarditis, pericardial effusion, or tamponade
- Radiation injury
- Renal insufficiency or failure
- Respiratory insufficiency or failure
- Restenosis or late acquired malapposition of treated segment
- Stent placement issues including geographic miss, malapposition, migration, or embolization
- Stent thrombosis / vessel occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Vessel injury (including access-site) such as spasm, lymphatic problems, pseudoaneurysm, arteriovenous fistula, trauma, dissection, occlusion, perforation, and rupture

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 MEGATRON Stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day, see Section 7.2, Pharmacokinetics). Adverse events associated with daily oral administration of everolimus (or potential adverse events not captured above, that may be unique to the everolimus drug coating) can be found in the labeling for finished pharmaceuticals containing everolimus, such as Afinitor or Zortress.

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 clinical assessments 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% 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	

BSC (MB IFU Template 8.2677 x 11.6929 A4, 92310060J), eIFU, MB, SYNERGY MEGATRON, en, 51466419-01A

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Parameter	SYNERGY (N=94)* ITT population
6 months	7.03±2.10
Intravascular ultrasound	
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
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).

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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 5-Year 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.

Table 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)

BSC (MB IFU Template 8.2677 x 11.6929 A4, 92310060J), eIFU, MB, SYNERGY MEGATRON, en, 51466419-01A
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	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)*
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 64.78±9.73 years 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% (3/466) 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)

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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

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 Intent-to-Treat 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.

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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 of 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[b]	*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 $P2Y_{12}$ 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.

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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.

Real World Evidence

The SYNERGY MEGATRON stent has been commercialized in Sweden since September 2019, 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 121-patient cohort treated with 143 SYNERGY MEGATRON stents, where additional stents placed during the index procedure included only Everolimus-eluting stents, and who had follow-up through 30 days, was identified. This complex patient population contained approximately 19% insulin treated diabetics, 19% current smokers, and 66% had acute coronary syndrome including 14% with STEMI. At 30 days, there were no instances of target lesion revascularization (TLR), stent thrombosis (ST) or restenosis in patients that were treated only with SYNERGY MEGATRON stents, with two revascularizations in the target vessel in multiple stented patients (1.4%). Results for the same cohort at 6 months showed a TLR rate of 2.9% in patients treated only with SYNERGY MEGATRON stents, and there were no instances of MI or stent thrombosis. Overall, the procedural, 30-day, and 6-month outcomes from the SCAAR registry demonstrate acceptable real-world use of the SYNERGY MEGATRON stent system, including 100% success for delivering all reported SYNERGY MEGATRON stents.

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 MEGATRON 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. In patients who are at a high risk of bleeding or who develop significant bleeding during DAPT treatment, the AHA/ACC 2016 guidelines suggest that a shorter DAPT duration may be reasonable.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, ischemic and bleeding risks, and patient preference. 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 and benefits including review of potential adverse events listed in this document, both for SYNERGY MEGATRON and for other interventional treatments likely to be employed.
- Discuss patient allergies, in particular the risk for patients who may be allergic to antiplatelet therapy, or to the stent components including everolimus, polymer, stainless steel, iron, nickel, molybdenum, chromium and/or platinum.
- Discuss the risks and benefits of antiplatelet therapy including risk of thromboembolism should the patient discontinue use.
- Discuss the conditions under which the patient can safely undergo MRI scanning (1.5 T and 3 T) after implant of a SYNERGY MEGATRON Stent.
- Discuss post-procedure instructions, including any follow-up appointments, lifestyle changes, medications, and home-care or rehabilitation guidelines.
- Instruct the patient to contact their healthcare provider if they develop any symptoms post-procedure, especially chest pain or access site pain or bleeding.
- Provide the patient with the completed implant card and advise the patient to carry the card with them at all times.
- Instruct the patient to present the implant card to their healthcare professionals (doctors, dentist, technicians) so they can take the necessary precautions.
- Advise the patient that additional information may be available to them on the Boston Scientific website (www.bostonscientific.com/patientlabeling).

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 under the Patient and Caregiver's section of the Boston Scientific website or by request) which includes information on coronary artery disease, the implant procedure and frequently asked questions.

Expected Lifetime

Inform the patient that the stent is a permanent implant - after the drug is eluted and the polymer is absorbed, the metallic stent scaffold remains. The stent scaffold has been tested for structural integrity (fracture resistance) for a minimum of 10 years; however, the materials of the stent scaffold are nonbiodegradable and are intended to last for the lifetime of the patient.

Note: It is estimated that the everolimus drug will be released into the surrounding arterial tissue for approximately 3 months following stent implantation. The bioabsorbable polymer is eliminated from the body as carbon dioxide and water through natural metabolic mechanisms. In vivo studies support that the polymer degradation is essentially complete by 4 months.

13 HOW SUPPLIED

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

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

Do not use if package is damaged or unintentionally opened before use.

Do not use if labeling is incomplete or illegible.

If damage is found, call your Boston Scientific representative.

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 AS THE FOIL POUCH IS 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: To minimize the risk of infection or microbial hazards after use, dispose device and packaging as follows:

After use, device and packaging may contain biohazardous substances. Any device and packaging that came into contact with biohazardous substances should be treated and disposed of as biohazardous waste or be treated and disposed of in accordance with any applicable hospital, administrative, and/or local government regulations. Use of a biohazardous container with biological hazard symbol is recommended. Untreated biohazardous waste should not be disposed of in the municipal waste system.

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 (sterile barrier) 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 MEGATRON Monorail Stent Delivery System, if the proximal shaft (hypotube) has been bent or kinked, do not continue to use the catheter.

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14.2 Additional Items for Safe Use (not included in Stent Delivery System package)

Quantity	Material
1	Appropriate guide catheter (see Table 2.1, SYNERGY MEGATRON 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 (sterile barrier) 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 the device 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.

5. Examine the device for any damage. If it is suspected that the sterility or integrity 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.
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 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 or soak the stent with sterile / isotonic 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 pressure 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 at atmospheric pressure (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.

Note: If a guide catheter extension is used, consideration should be given to the appropriate guide catheter compatibility (see Table 2.1 SYNERGY MEGATRON Stent System Product Description), as a larger guide catheter may be required. Use of guide catheter extension devices reduces the lumen available for catheter manipulation.

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. Fully cover the entire lesion and balloon treated area. The stent should adequately cover healthy vessel proximal and distal to the lesion. If the position of the stent is not optimal, it should be carefully repositioned or removed (See also Precautions – Section 6.13, 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 6.13, 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 16 atm (1620 kPa) (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 diameters. Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall apposition should be verified through intravascular imaging.
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 or post-dilation balloon catheter visually confirm complete balloon deflation under fluoroscopy.
7. If more than one SYNERGY MEGATRON 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 MEGATRON 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, or exchange the stent delivery system with a larger post- dilation balloon catheter.

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 or post-dilation balloon catheter 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 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.

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Nominal Stent Diameter (ID)	Post-Dilation Limits (ID)*
3.50 mm, 4.00 mm, 4.50 mm, 5.00 mm	6.00 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 6.14, Post-Procedure: Care must be exercised when crossing a recently deployed stent with any wire, catheter or ancillary device to avoid disrupting the stent placement, apposition, geometry, and/or coating. If recrossing with a guidewire, the stented segment should be recrossed carefully with a prolapsed tip to avoid dislodging the stent.

Note: In calcified lesions ensure balloon expansion in the distal stented segment fully apposes the stent to the vessel wall (particularly with non-compliant balloons).

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

14.4 Compatibility Information for Two Devices in a Guide Catheter

6F (1.78 mm) compatibility: Any combination of one SYNERGY MEGATRON Stent (3.50 mm to 5.00 mm) and one balloon catheter (NC EMERGE 3.25 mm x 20 mm or smaller*), can be used simultaneously within a 6F Guide Catheter (min ID 1.78 mm / 0.070 inch).* or other Boston Scientific coronary balloon catheter with the same shaft outer dimensions.

Note: Consideration should be given to the appropriate guide catheter compatibility if utilizing multiple interventional devices within the one guide catheter, as a larger guide catheter may be required.

Note: Use of guide catheter extension devices reduces the lumen available for catheter manipulation.

14.5 Post-Procedure

It is very important that the patient be compliant with post-procedural antiplatelet recommendations given by their physician.

- If the patient requires MRI imaging, see Section 6.10, Magnetic Resonance Imaging (MRI).
- Any serious incident that occurs in relation to this device should be reported to the manufacturer and relevant local regulatory authority.

14.6 In Vitro Information

Table 14.1 Typical SYNERGY MEGATRON Stent System Compliance

Pressure atm (kPa)	Stent Inner Diameters (mm)			
	3.50	4.00	4.50	5.00
8 (814)	3.18	3.64	4.13	4.59
9 (910)	3.29	3.76	4.26	4.73
10 (1014)	3.38	3.87	4.37	4.86
11 (1117) *	3.48	3.98	4.49	4.97
12 (1213)	3.56	4.07	4.59	5.07
13 (1317)	3.63	4.15	4.67	5.16
14 (1420)	3.69	4.21	4.75	5.24
15 (1517)	3.74	4.27	4.80	5.30
16 (1620) **	3.78	4.32	4.87	5.36
17 (1724)	3.83	4.37	4.92	5.42
18 (1827)	3.87	4.41	4.97	5.47
19 (1924)	3.93	4.47	5.04	5.52
20 (2027)	3.98	4.53	5.10	5.57

* Nominal pressure = 11 atm (1117 kPa)
** 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 16 atm (1620 kPa).

15 WARRANTY

For device warranty information, visit (www.bostonscientific.com/warranty).

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16 SYMBOL DEFINITIONS

Commonly used medical device symbols that appear on the labeling are defined at www.bostonscientific.com/SymbolsGlossary.

Additional symbols are defined at the end of this document.

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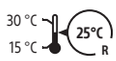
Contents

Maximum Stent Inner Diameter

Recommended Guide Catheter

Recommended Guidewire



Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

Protect from Humidity

Push Here To Open

EC REP

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