EVOLVE 48 (S2356)

A Prospective Multicenter Single Arm Trial to Assess the Safety and Effectiveness of the SYNERGY™ 48 mm Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY™ Stent System) for the Treatment of Subjects with Atherosclerotic Lesion(s)

CLINICAL INVESTIGATION PLAN

Sponsored By

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Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to investigational sites.

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Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
A	**October 16, 2017**	**90702637 Rev./Ver. AH**			**Initial Release**

2. Protocol Synopsis

EVOLVE 48 (S2356) A Prospective Multicenter Single Arm Trial to Assess the Safety and Effectiveness of the SYNERGY™ 48 mm Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY™ Stent System) for the Treatment of Subjects with Atherosclerotic Lesion(s)	
Study Objective(s)	To assess the FDA requirement for safety and effectiveness of the SYNERGY 48 mm Coronary Stent System for the treatment of subjects with atherosclerotic lesion(s) > 34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate). Sites outside the United States (US) are being included in this protocol to collect additional 48 mm data to support future FDA approval. This is also an opportunity to collect EU post-market safety and performance data for the current CE Marked 48 mm device.
Test Device	SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY ™ Stent System)
Device Sizes	The SYNERGY 48 device matrix consists of the following sizes (stent diameter and stent length): 2.50 mm x 48 mm 2.75 mm x 48 mm* 3.00 mm x 48 mm 3.50 mm x 48 mm 4.00 mm x 48 mm *2.75 x 48 mm will not be included in the investigational device matrix in the United States (US)
Study Design	Prospective, open label, single arm, multi-center
Planned Number of Subjects	Up to 100 subjects
Planned Number of Investigational	Up to 20 sites in the United States, Europe and New Zealand

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Sites / Countries	
Primary Safety and Effectiveness Endpoint(s)	The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, defined as any ischemia-driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death.
Additional Endpoints	Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months and 2 years. • TLR rate, TLF rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate • Target vessel failure (TVF) rate • MI (Q-wave and non–Q-wave) rate • Cardiac death rate, Non-cardiac death rate • All death rate • Cardiac death or MI rate • All death or MI rate • All death/MI/TVR rate • Stent thrombosis rates (by Academic Research Consortium [ARC] definitions) Periprocedural endpoints: • Technical success rate • Clinical procedural success rate
Follow-up Schedule	Clinical follow-up: in-hospital, 30 days, 6 months, 12 months and 2 years after the index procedure. The study will be considered complete with regard to the primary endpoint after all subjects have completed the 12-month follow-up period. Subjects who are enrolled but who do not receive a study stent will be followed through 12 months only.

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Study Duration	Enrolled subjects who receive a SYNERGY stent will be followed for 2 years following the index procedure.
Antiplatelet Therapy	**Aspirin**: • Subjects must be treated with aspirin for the duration of the trial. The minimum daily maintenance dose of aspirin should be 75 mg –100 mg. **P2Y12 inhibitor**: • Subjects must be treated with one of the following P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor). The dose and duration should be based on current guidelines. o In subjects with stable ischemic heart disease (SIHD) P2Y12 inhibitor therapy should be given for at least 6 months post stent implantation. For subjects at high risk of bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable. o In subjects with acute coronary syndrome (ACS) P2Y12 inhibitor therapy should be given for at least 12 months. For subjects at high risk of bleeding, discontinuation of P2Y12 inhibitory therapy after 6 months may be reasonable. • For subjects who have been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is not required. For subjects who have not been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is recommended.
Safety Parameters	• All serious adverse events (SAE), adverse device effects (ADE), death, MI, TVR and stent thrombosis will be collected for all enrolled subjects through end of study • A clinical events committee (CEC) will adjudicate all endpoint events, as specified in the CEC Charter
Clinical Inclusion Criteria	CI1. Subject must be at least 18 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed

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	CI3. Subject is eligible for percutaneous coronary intervention (PCI) and is an acceptable candidate for coronary artery bypass grafting (CABG) CI4. Subject has either: Symptomatic coronary artery disease with one of the following: stenosis ≥ 70%, abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure OR Documented silent ischemia based on one of the following: abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure CI5. Subject is willing to comply with all protocol-required follow-up evaluation
Angiographic Inclusion Criteria	AI1. Target lesion must be located in a native coronary artery with a visually estimated reference vessel diameter (RVD) ≥2.5 mm and ≤4.0 mm AI2. Target lesion length must be >34 mm and ≤44 mm (by visual estimate) AI3. Target lesion must have visually estimated stenosis ≥50% and <100% with thrombolysis in Myocardial Infarction (TIMI) flow >1 AI4. Coronary anatomy is likely to allow delivery of a study device to the target lesion AI5. The target lesion must be successfully predilated/pretreated. If a non-target lesion is treated, it should be treated first and should be deemed an angiographic success ***Note:*** Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI. ***Note:*** Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring

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	balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C.
Clinical Exclusion Criteria	CE1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI) CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure CE5. Planned PCI (including staged procedures) or CABG after the index procedure CE6. Subject previously treated at any time with intravascular brachytherapy CE7. Subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the trial stent system or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel, everolimus or structurally related compounds, polymer or individual components, all $P2Y_{12}$ inhibitors, or aspirin) CE8. Subject has one of the following (as assessed prior to enrollment): o Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 24 months o Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) o Planned procedure that may cause non-compliance with the protocol or confound data interpretation CE9. Subject is receiving chronic (≥72 hours) anticoagulation therapy (i.e., heparin, coumadin) for indications other than acute coronary syndrome CE10. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3

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	CE11. Subject has a white blood cell (WBC) count < 3,000 cells/mm^3 CE12. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis CE13. Subject is on dialysis or has baseline serum creatinine level >2.0 mg/dL (177µmol/L) CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding CE17. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) at the time of the index procedure CE18. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint CE19. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure CE20. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure) CE21. Subject is a woman who is pregnant or nursing
Angiographic Exclusion Criteria	AE1. Subject has more than 1 target lesion, or more than 1 target lesion and 1 non-target lesion, which will be treated during the index procedure ***Note***: Multiple focal stenoses will be considered as a single lesion if they can be completely covered with 1 study stent AE2. Treatment of lesions in more than 2 major epicardial vessels ***Note*****:** 1 target lesion in the target vessel and 1 non-target lesion in non-target vessel is allowed AE3. Subject has unprotected left main coronary artery disease (>50% diameter stenosis)

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	AE4. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon atherectomy) within 24 hours prior to the index procedure AE5. Thrombus, or possible thrombus, present in the target vessel (by visual estimate) AE6. **Target lesion** meets any of the following criteria: • Treatment of a single lesion with more than 1 stent • Left main location • Lesion is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate • Lesion is located within a saphenous vein graft or an arterial graft • Lesion will be accessed via a saphenous vein graft or arterial graft • Lesion with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing • Lesion treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent) • Lesion is restenotic from a previous stent implantation or study stent would overlap with a previous stent AE7. **Non-target lesion** meets any of the following criteria: • Located within the target vessel • Left main location • Lesion is located within a saphenous vein graft or an arterial graft • Lesion with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing • Lesion treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent) • Requires additional unplanned stents (treatment of the non-target lesion with more than one stent is permitted as long as the stents

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	are initially planned) • Treatment not deemed an angiographic success ***Note:*** Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.
Multiple Interventions During Index Procedure	Up to 2 native coronary artery lesions in 2 major epicardial vessels may be treated. Subjects may have 1 target lesion, or 1 target lesion and 1 non-target lesion treated. • One lesion must meet the angiographic criteria for a target lesion as described above, and is appropriate to be treated with a SYNERGY 48 mm coronary stent. • A maximum of 1 non-target lesion in 1 non-target vessel may be treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure. If stenting is appropriate for the treatment of a non-target lesion, an everolimus-eluting stent should be used. The non-target vessel should be treated during the index procedure prior to the treatment of the target lesion and deemed an angiographic success.
Statistical Methods	
Primary Statistical Hypothesis	The 12-month TLF rate for SYNERGY subjects is less than the performance goal (PG). H_0: $P_{SYNERGY} \geq PG$ H_1: $P_{SYNERGY} < PG$ where $P_{SYNERGY}$ is the 12-month TLF rate for subjects with 48 mm SYNERGY stent and PG is a performance goal.
Statistical Test Method	A one-group Clopper-Pearson exact test will be used to test whether the 12-month TLF rate for SYNERGY is less than a PG.
Success Criteria for the Primary	If the *P* value from the one-sided Clopper-Pearson test is <0.05, the 48 mm SYNERGY stent is concluded to meet the PG with respect to the

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Statistical Hypothesis Test	12-month TLF rate. This corresponds to the one-sided 95% upper confidence bound on the observed 12-month TLF rate from SYNERGY being less than the PG.
Sample Size Parameters	• Expected 12-month TLF rate for SYNERGY = 9.2% • PG = 19.5% (expected control rate of 13% + delta of 6.5%) • Test significance level (α) = 0.05 (1-sided) • Power ($1-\beta$) ≥ 0.80 • N = 95 evaluable patients • Expected attrition rate = 5% • N=100 enrolled patients

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3.1. *Table of Figures*

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4. Introduction

The EVOLVE 48 trial is designed to assess the FDA requirement for safety and effectiveness of the SYNERGY 48 mm Coronary Stent System for the treatment of subjects with atherosclerotic lesion(s) > 34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate). Sites outside the United States are being included in this protocol to collect additional 48 mm data to support future FDA approval. This is also an opportunity to collect EU post-market safety and performance data for the current CE Marked 48 mm device. The SYNERGY Stent System represents the next generation drug-eluting stent (DES) from Boston Scientific Corporation (BSC, Marlborough Massachusetts, United States). The Stent System is based on the well characterized Element™ stent platform and utilizes a bioabsorbable poly(DL-lactide-co-glycolide) (PLGA) polymer to deliver everolimus. The SYNERGY stent incorporates a number of features designed to improve vascular healing and thus potentially reduce the risk of late stent thrombosis and the need for prolonged dual antiplatelet therapy. First, the polymer coating is only applied to the abluminal surface of the stent. The inside surface of the stent - the side in contact with the bloodstream – is bare metal. Second, the polymer degrades within 4 months leaving only the biologically inert bare-metal platform behind (1).

The SYNERGY stent system is approved and commercially available in the following sizes (stent diameter and length) as shown in the following device matrix. In addition, the 48 mm length stent is CE marked.

		Length							
		8 mm	**12 mm**	**16 mm**	**20 mm**	**24 mm**	**28 mm**	**32 mm**	**38 mm**
Diameters	**2.25 mm**	X	X	X	X	X	X	X	X
	2.50 mm	X	X	X	X	X	X	X	X
	2.75 mm	X	X	X	X	X	X	X	X
	3.00 mm	X	X	X	X	X	X	X	X
	3.50 mm	X	X	X	X	X	X	X	X
	4.00 mm	X	X	X	X	X	X	X	X

The availability of a 48 mm SYNERGY stent would reduce the need for overlapping stents. When long lesions were treated with 1 long stent instead of 2 shorter, overlapping stents, intervention time was less, the need for a contrast agent had a tendency to be lower, and procedural costs were significantly less (2).

4.1. *Clinical Development Program for SYNERGY*

The safety and effectiveness of the Element stent platform in combination with everolimus in the form of the PROMUS Element stent has been established in the PLATINUM Clinical Trial Program (3-18). The EVOLVE series of trials including EVOLVE, EVOLVE II, and EVOLVE II QCA, have established the safety and effectiveness of the SYNERGY Stent System for the treatment of coronary artery lesions.

4.1.1. **EVOLVE First Human Use (FHU) Clinical Trial**

The EVOLVE trial is a prospective, randomized, multicenter, single-blind, non-inferiority trial evaluating the safety and performance of two dose formulations of the SYNERGY stent, SYNERGY FHU stent (dose and release profile similar to PROMUS Element) and SYNERGY FHU (1/2 Dose) stent (similar release profile and half the dose of PROMUS Element) in 291 subjects for the treatment of de novo lesions ≤28 mm in length in a native coronary artery 2.25–3.5 mm (visual estimate). The primary clinical endpoint of the EVOLVE trial was the 30-day TLF rate defined as a composite of cardiac death or MI related to the target vessel, or ischemia-driven TLR. The primary angiographic endpoint was in-stent late loss as measured by QCA at 6 months. The 30-day TLF rate was 0%, 1.1%, and 3.1% in the PROMUS Element, SYNERGY FHU, and SYNERGY FHU (1/2 Dose) groups respectively. All TLF events in the SYNERGY groups were attributable to target vessel related periprocedural non-Q-wave MIs. At 6 months, the TLF rate was 3.1%, 2.2%, and 4.1% in the PROMUS Element, SYNERGY FHU, and SYNERGY FHU (1/2 Dose) groups respectively. Through 6 months, there were no Q-wave MIs, cardiac deaths, or stent thromboses in any group. The 6-month primary angiographic endpoint of in-stent late loss was 0.15±0.34 mm, 0.10±0.25 mm, and 0.13±0.26 mm for PROMUS Element, SYNERGY FHU, and SYNERGY FHU (1/2 Dose) respectively. The upper one-sided 95.2% confidence limit of the difference between test and control for SYNERGY FHU was 0.02 and SYNERGY FHU (1/2 Dose) was 0.05; both lower than the pre-specified non-inferiority margin of 0.20 mm (*P* for non-inferiority <0.001) (19). At 12-months, there were no significant differences between groups in TLF, MI, and revascularization rates and there were no cardiac deaths, Q-wave MIs, or stent thromboses in any group (20,21). The study is now considered complete with regard to the primary endpoint and follow-up through 5 years is complete.

The final 5-year results of EVOLVE demonstrate no significant differences between groups with respect to TLF, cardiac death or MI.

- Trend toward lower rates of TLR with SYNERGY vs PROMUS Element
- No definite/probable stent thrombosis in any group at 5 years

These results support the safety and efficacy of the novel abluminal bioabsorbable polymer SYNERGY everolimus-eluting stent for the treatment of patients with de novo coronary artery disease(22).

4.1.2. **EVOLVE II Clinical Program**

The SYNERGY stent is currently being evaluated in the EVOLVE II global clinical program for the treatment of subjects with a maximum of 3 de novo atherosclerotic lesions. The program includes the EVOLVE II trial, which comprises a randomized controlled trial (RCT) with single-arm diabetic (DM) and pharmacokinetic (PK) substudies, and the EVOLVE II Quantitative Coronary Angiography (QCA) study as detailed below and in **Table 4.1-1**.

- The randomized controlled trial (RCT) at 125 global centers enrolled 1,684 subjects (1:1 randomization of SYNERGY to PROMUS Element Plus) with a maximum of 3 atherosclerotic lesions ≤34 mm in length (by visual estimate) in native coronary arteries ≥2.25 mm to ≤4.0 mm in diameter (by visual estimate). This study completed enrollment in August, 2013 and follow-up continues through 5 years.

  The RCT primary endpoint of 12-month target lesion failure (TLF), defined as ischemia-driven target lesion revascularization (TLR), target vessel-related MI, or cardiac death, was observed in 6.7% of SYNERGY and 6.5% PROMUS Element Plus treated subjects by intention-to-treat analysis (p=0.0005 for non-inferiority) and 6.4% in both groups by per protocol analysis (p=0.0003 for non-inferiority). With respect to 1-year TLF SYNERGY is non-inferior to PROMUS Element Plus. Clinically-indicated TLR and definite/probable stent thrombosis were observed in 2.6% vs 1.7% (p=0.21) and 0.4% vs 0.6% (p=0.50) of SYNERGY vs. PROMUS Element Plus treated subjects, respectively (24).

- A concurrent, non-randomized, diabetic (DM) substudy at 48 global centers enrolled an additional 203 SYNERGY diabetic subjects with atherosclerotic lesions ≤ 34 mm in length (by visual estimate) in native coronary arteries ≥ 2.25 mm to ≤ 4.0 mm in diameter (by visual estimate). Enrollment was complete in December, 2013 and follow-up continues through 5 years.

  In the EVOLVE II Diabetes Substudy, diabetic subjects randomized to the SYNERGY arm in the EVOLVE II RCT (263 subjects) were pooled with diabetic subjects enrolled in the single-arm DM substudy (203 subjects) for a total of 466 diabetic subjects treated with SYNERGY stents. The primary endpoint of 12-month TLF was met. In the intention-to-treat analysis, the rate of TLF was 7.5% in SYNERGY treated diabetic subjects which is significantly less than the performance goal (14.5%; $P<0.0001$). Definite or probable stent thrombosis occurred in 1.1% of subjects (25,26).

- A concurrent, non-randomized, pharmacokinetic (PK) substudy at 6 centers enrolled 21 subjects with atherosclerotic lesions ≤ 34 mm in length (by visual estimate) in native coronary arteries ≥ 2.25 mm to ≤ 4.0 mm in diameter (by visual estimate) to evaluate everolimus blood levels following stent implantation. Enrollment was complete in October, 2013.

- The EVOLVE II QCA study was a prospective, single-arm, multicenter, observational study that enrolled 100 subjects at 12 centers with atherosclerotic lesion(s) ≤34 mm in length (by visual estimate) in native coronary arteries ≥2.25 mm to ≤4.0 mm in diameter (by visual estimate). Enrollment was complete in October,

2013 and the final follow-up visit occurred in October 2014; the trial is now complete.

The EVOLVE II QCA primary endpoint analysis of in-stent late loss at 9 months post-index procedure, was 0.23±0.34 mm (in 95 subjects) which was significantly less than the performance goal of 0.40 mm ($p<0.0001$). There were no deaths and no subject experienced a definite, probable or possible stent thrombosis through 12 months. Five subjects had peri-procedural non-Q-wave myocardial infarctions (5.0%) according to the protocol definition (with peri-procedural MI defined based on CK-MB >3x URL) (27).

Table 4.1-1: Summary of the EVOLVE II Global Clinical Program

Trial Name	EVOLVE II RCT	EVOLVE II DM substudy	EVOLVE II PK substudy	EVOLVE II QCA
Design	1:1 Randomization SYNERGY vs. PROMUS Element Plus	Single Arm	Single Arm	Single Arm
Vessel (mm)	≥2.25 to ≤4.0	≥2.25 to ≤4.0	≥2.25 to ≤4.0	≥2.25 to ≤4.0
Lesion Length (mm)	≤34	≤34	≤34	≤34
Sample Size	1684 (846 SYNERGY; 838 PROMUS Element Plus)	203	21	100
Primary Endpoint	12 Month TLF	12 Month TLF	Observational	9 month In-Stent Late Loss (mm)
Primary Endpoint Result (SYNERGY)[1]	6.7% (55/826)	7.5% (34/451)	Not Applicable	0.23±0.34

Abbreviations: DM=diabetic, PK=pharmacokinetics; QCA=quantitative coronary angiography; RCT=randomized controlled trial; TLF=target lesion failure (target vessel-related cardiac death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization)
1: Based on intent-to-treat analysis

4.1.3. **Summary**

Safety and efficacy of the SYNERGY Stent System has been demonstrated in the EVOLVE Clinical Program. The SYNERGY stent has unique characteristics, and is designed to complete resorption of the polymer shortly following the drug elution at 90 days. The EVOLVE 48 trial is designed to assess the safety and effectiveness of the SYNERGY 48 mm Coronary Stent System for the treatment of subjects with atherosclerotic lesion(s) > 34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate).

5. Device Description

5.1. *SYNERGY Device*

The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System), manufactured by BSC, is a device/drug combination product comprised of two regulated components: a device (Coronary Stent System) and a drug product (a formulation of everolimus contained in a bioabsorbable polymer coating).

The SYNERGY Stent System is approved for use and commercially available in sizes 2.25 mm - 4.0 mm in diameter and 8 mm - 38 mm in length. Additionally, it is CE marked in the 48 mm length.

Device Component Description

The SYNERGY Stent System consists of a platinum chromium stent platform with an abluminal drug/polymer coating mounted onto a Monorail Delivery System. The SYNERGY 48 device matrix consists of the following sizes (stent diameter and stent length):

- 2.50 mm x 48 mm
- 2.75 mm x 48 mm*
- 3.00 mm x 48 mm
- 3.50 mm x 48 mm
- 4.00 mm x 48 mm

*2.75 x 48 mm will not be included in the investigational device matrix in the US

5.1.1. **Drug/Polymer Component Description**

5.1.1.1. Everolimus

The active pharmaceutical ingredient in the SYNERGY Stent is everolimus. The everolimus chemical name is 40-0-(2-hydroxyethyl)-rapamycin. Everolimus has been evaluated in clinical trials in the US and Europe for use in conjunction with other medications to prevent heart and renal transplant rejection. Everolimus used as an active ingredient on coronary stents has been shown to prevent restenosis in clinical trials.

5.1.1.2. Polymer Carrier

The SYNERGY stent is coated on the abluminal stent surface with a bioabsorbable drug matrix. The bioabsorbable drug matrix is composed of PLGA mixed with everolimus.

5.2. *Device Labeling*

5.2.1. **Region – US**

A copy of the DFU for the SYNERGY stent is included in the EVOLVE 48 study Manual of Operations. The study devices are labeled on the front, back, and side of the outer cartons, and on the outside foil and inside sterile pouch. Packaging will include peelable, self-

adhesive labels for each unit of product shipped. The labeling will include the following information.

- Product Name
- Catalog Number and Universal Part Number (UPN)
- Global Trade Item Number (GTIN)
- Serial or tracking identification number
- Lot number
- Stent dimensions (stent diameter and stent length in mm)
- Expiration (use by) date

The following statements appear on the SYNERGY study device product labeling for clinical US distribution.

Caution: Investigational Device. Limited by United States law to investigational use. Exclusively for Clinical Investigations.

5.2.2. **Region – Outside US**

In regions where the SYNERGY 48 mm is commercially available it will be labeled per approved regulations. A copy of the DFU for the study stent, SYNERGY 48 mm, is contained in each product package. The devices are labeled on the front, back, and side of the outer cartons, and on the outside foil and inside sterile pouch. Packaging will include peelable, self-adhesive labels for each unit of product shipped. The labeling will include the following information.

- Product Name
- Catalog Number and Universal Part Number (UPN)
- Global Trade Item Number (GTIN)
- Lot number
- Stent dimensions (stent diameter and stent length in mm)
- Expiration (use by) date

6. Study Objectives

To assess the FDA requirement for safety and effectiveness of the SYNERGY 48 mm Coronary Stent System for the treatment of subjects with atherosclerotic lesion(s) > 34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate).

Sites outside the United States are being included in this protocol to collect additional 48 mm data to support future FDA approval. This is also an opportunity to collect EU post-market safety and performance data for the current CE Marked 48 mm device.

7. Study Endpoints

The primary and additional endpoints will be evaluated for all subjects who are enrolled in the trial, whether or not a study stent is implanted.

7.1. *Primary Endpoint*

The primary endpoint is the 12-month Target Lesion Failure (TLF) rate, defined as any ischemia-driven revascularization of the target lesion (TLR), myocardial infarction (MI, Q-wave and non–Q-wave) related to the target vessel, or cardiac death.

7.2. *Additional Endpoints*

Clinical endpoints measured in-hospital and at 30 days, 6 months, 12 months and 2 years.

- TLR rate, TLF rate (primary endpoint at 12 months), Target vessel revascularization (TVR) rate
- Target vessel failure (TVF) rate
- MI (Q-wave and non–Q-wave) rate
- Cardiac death rate, Non-cardiac death rate
- All death rate
- Cardiac death or MI rate
- All death or MI rate
- All death/MI/TVR rate
- Stent thrombosis rates (by Academic Research Consortium [ARC] definitions)

Periprocedural endpoints:

- Technical success rate
- Clinical procedural success rate

8. Study Design

The EVOLVE 48 Study is a prospective, multicenter, open label, single-arm study to assess the safety and effectiveness of the SYNERGY 48 mm stent for the treatment of atherosclerotic lesion(s).

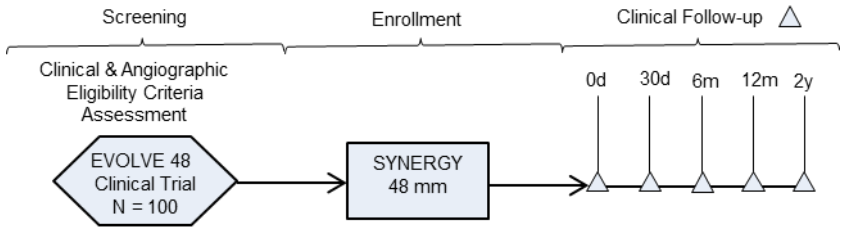
8.1. *Scale and Duration*

The EVOLVE 48 Study will be conducted at up to 20 sites in the United States, Europe and New Zealandwith planned enrollment of 100 subjects. All subjects will be screened according to the protocol inclusion and exclusion criteria.

Clinical follow-up will be required at the following time points: in hospital, 30 days, 6 months, 12 months and 2 years post index procedure.

A schematic of the EVOLVE 48 trial design is shown in Figure 8.1-1

Figure 8.1-1: EVOLVE 48 Study Design



8.2. *Treatment Assignment*

Once the subject has met all clinical inclusion and no clinical exclusion criteria, the subject should be considered eligible to be enrolled in the trial. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure. If the subject is found to meet the inclusion criteria during the angiographic phase of the procedure, the subject will be considered eligible to be enrolled.

Subjects in this trial will not be randomized. Subjects will be considered enrolled after the subject has signed the IRB/IEC approved study informed consent form (ICF) and successful predilation /pretreatment of the target lesion and insertion of a 48 mm SYNERGY stent into the introducer sheath. If a non-target lesion is treated, it should be treated first and should be deemed to be an angiographic success.

Subjects will be treated with The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System), 48 mm in length; refer to Section 5.0 (Device Description) for study device product matrix.

8.2.1. **Target and Non-target Lesions**

A target lesion is the lesion selected by the Investigator for treatment with the study stent. The target lesion includes the arterial segment treated with the study stent plus the arterial segment 5 mm proximal and 5 mm distal to the treatment site. The target lesion must meet all the angiographic selection criteria.

Up to 2 native coronary artery lesions in 2 major epicardial vessels may be treated. One lesion must meet the angiographic criteria described above, and is appropriate to be treated with a SYNERGY 48 mm coronary stent. A maximum of 1 non-target lesion in 1 non-target vessel may be treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure. If stenting is appropriate for the treatment of a non-target lesion, an everolimus-eluting stent should be used. The non-target lesion should be treated first and should be deemed an angiographic success prior to the treatment of the target lesion.

Note: Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.

Note: Multiple focal stenoses will be considered as a single lesion if they can be completely covered with 1 study stent.

Predilitation/pretreatment of the target lesion is required in this trial. If the target lesion is not successfully predilated/pretreated, the subject should not be enrolled. If a non-target lesion is to be treated, it should be treated first and must be deemed an angiographic success. Following the successful treatment of the non-target lesion, predilation of the target lesion may then be performed.

Note: Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C

8.3. *Justification for the Study Design*

The EVOLVE 48 trial will evaluate the FDA requirement for safety and effectiveness of the SYNERGY stent for the treatment of subjects with atherosclerotic lesion(s) > 34 mm and ≤ 44 mm in length (by visual estimate) in native coronary arteries ≥2.5 mm to ≤4.0 mm in diameter (by visual estimate). Safety and performance has been demonstrated for this stent in the following sizes which have received CE mark and FDA approval and is commercially available in other regions.

		Length							
		8 mm	**12 mm**	**16 mm**	**20 mm**	**24 mm**	**28 mm**	**32 mm**	**38 mm**
Diameters	**2.25 mm**	X	X	X	X	X	X	X	X
	2.50 mm	X	X	X	X	X	X	X	X
	2.75 mm	X	X	X	X	X	X	X	X
	3.00 mm	X	X	X	X	X	X	X	X
	3.50 mm	X	X	X	X	X	X	X	X
	4.00 mm	X	X	X	X	X	X	X	X

Sites outside the United States are being included in this protocol to collect additional data to support future FDA approval of the 48 mm diameter. This is also an opportunity to collect EU post-market safety and performance data for the current CE Marked 48 mm device.

During the trial, P2Y12 inhibitors will be administered based on current guidelines and aspirin use will be required for the duration of the trial post index procedure. Ongoing dynamic data safety monitoring will be performed throughout the trial to minimize subject risk. All enrolled subjects receiving the study stent will be followed for 2 years post index procedure.

Given that the predictors of the key outcomes of interest are well-understood and there is limited residual between-trial variation, a prospective single arm study has been proposed for the EVOLVE 48 Study.

9. Subject Selection

9.1. *Study Population and Eligibility*

Clinical and angiographic inclusion and exclusion criteria for the EVOLVE 48 trial are included in **Table 9.2-1** and **Table 9.3-1** respectively. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the clinical or angiographic exclusion criteria

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 9.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Table 9.3-1**) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	CI1. Subject must be at least 18 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed CI3. Subject is eligible for percutaneous coronary intervention (PCI) and is an acceptable candidate for coronary artery bypass grafting (CABG) CI4. Subject has either: Symptomatic coronary artery disease with one of the following: stenosis ≥ 70%, abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure OR Documented silent ischemia based on one of the following: abnormal fractional flow reserve (FFR), abnormal stress or imaging stress test, or elevated biomarkers prior to the procedure CI5. Subject is willing to comply with all protocol-required follow-up evaluation
Angiographic Inclusion Criteria (visual	AI1. Target lesion must be located in a native coronary artery with a visually estimated reference vessel diameter (RVD) ≥2.5 mm and ≤4.0 mm AI2. Target lesion length must be >34 mm and ≤44 mm (by visual estimate)

estimate)	AI3. Target lesion must have visually estimated stenosis ≥50% and <100% with thrombolysis in Myocardial Infarction (TIMI) flow >1 AI4. Coronary anatomy is likely to allow delivery of a study device to the target lesion AI5. The target lesion must be successfully predilated/pretreated. If a non-target lesion is treated, it should be treated first and should be deemed an angiographic success ***Note:*** Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI. ***Note:*** Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C.

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 9.3-1**) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	CE1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI) CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure CE5. Planned PCI (including staged procedures) or CABG after the index procedure CE6. Subject previously treated at any time with intravascular brachytherapy CE7. Subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the trial stent system or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel,

	everolimus or structurally related compounds, polymer or individual components, all $P2Y_{12}$ inhibitors, or aspirin) CE8. Subject has one of the following (as assessed prior to enrollment): o Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 24 months o Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) o Planned procedure that may cause non-compliance with the protocol or confound data interpretation CE9. Subject is receiving chronic (≥72 hours) anticoagulation therapy (i.e., heparin, coumadin) for indications other than acute coronary syndrome CE10. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 CE11. Subject has a white blood cell (WBC) count < 3,000 cells/mm^3 CE12. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis CE13. Subject is on dialysis or has baseline serum creatinine level >2.0 mg/dL (177µmol/L) CE14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions CE15. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months CE16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding CE17. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) at the time of the index procedure CE18. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint CE19. Subject intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure CE20. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure) CE21. Subject is a woman who is pregnant or nursing
Angiographic Exclusion	AE1. Subject has more than 1 target lesion, or more than 1 target lesion and 1 non-target lesion, which will be treated during the index procedure

Criteria (visual estimate)	***Note***: Multiple focal stenoses will be considered as a single lesion if they can be completely covered with 1 study stent AE2. Treatment of lesions in more than 2 major epicardial vessels ***Note*****:** 1 target lesion in the target vessel and 1 non-target lesion in non-target vessel is allowed AE3. Subject has unprotected left main coronary artery disease (>50% diameter stenosis) AE4. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon atherectomy) within 24 hours prior to the index procedure AE5. Thrombus, or possible thrombus, present in the target vessel (by visual estimate) AE6. **Target lesion** meets any of the following criteria: • Treatment of a single lesion with more than 1 stent • Left main location • Lesion is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate • Lesion is located within a saphenous vein graft or an arterial graft • Lesion will be accessed via a saphenous vein graft or arterial graft • Lesion with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing • Lesion treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent) • Lesion is restenotic from a previous stent implantation or study stent would overlap with a previous stent AE7. **Non-target lesion** meets any of the following criteria: • Located within the target vessel • Left main location • Lesion is located within a saphenous vein graft or an arterial graft • Lesion with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing • Lesion treated during the index procedure that involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than 1 stent)

	• Requires additional unplanned stents (treatment of the non-target lesion with more than one stent is permitted as long as the stents are initially planned) • Treatment not deemed an angiographic success ***Note:*** Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.

10. Subject Accountability

10.1. *Point of Enrollment*

Once the subject has met all clinical inclusion and no clinical exclusion criteria, the subject should be considered eligible to be enrolled in the trial. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure. If the subject is found to meet the inclusion criteria during the angiographic phase of the procedure the subject will be considered eligible to be enrolled. Subjects will be considered enrolled after the subject has signed the IRB/IEC approved study informed consent form (ICF) and successful predilation /pretreatment of the target lesion and insertion of the stent in the introducer sheath. If a non-target lesion is treated, it should be treated first and should be deemed an angiographic success.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While trial withdrawal is discouraged, subjects may choose to withdraw from the trial at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional trial follow-up, nor will they be replaced (the justified sample size considers an estimated allowance for attrition). The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The Investigator may discontinue a subject from participation in the trial if the Investigator feels that the subject can no longer fully comply with the requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

10.3. *Enrollment Controls*

The EVOLVE 48 trial will implement a formal Enrollment Communication Plan. The plan will outline the specific activities and responsibilities of BSC employees and representatives, and nature and timing of communications to Investigators as enrollment draws to a close. The objective of the plan is to minimize the risk of enrollment beyond the protocol-specified enrollment cap of 100 subjects.

11. Study Methods

11.1. *Data Collection*

The data collection schedule for the SYNERGY 48 mm trial is summarized in **Table 11.1-1**.

Table 11.1-1: Data Collection Schedule

	Baseline/ Procedure/ Discharge	Follow-up Visits			
		30 Days (±7 Days)[b]	6 Months (±30 Days)[b]	12 Months (±30 Days)[b]	2 Years (±30 Days)[b]
Informed consent form, including informed consent signature date[a]	X				
Demographics, including age, gender, and race and ethnicity (unless restricted by local laws)	X				
Medical history, including diabetes mellitus status[c]	X				
Angina assessment	X	X	X	X	X
Cardiac enzymes[d,e,f]	X				
Antithrombotic medications	X				
Antiplatelet medications	X	X	X	X	X
Most recent previous PCI procedure information	X				
Procedural, target lesion, non-target lesion (if applicable) predilatation, postdilatation (if applicable), and study stent information	X				
Angiography	X				
ADE, SAE, SADE, UADE, USADE, all CEC events inclusive of death, MI, TVR and stent thrombosis and device deficiency assessment[g]	X	X	X	X	X

a: If the study Informed Consent Form is modified during the course of the trial, study subjects will be re-consented, if necessary
b: All follow-up dates will be calculated from the date of the index procedure. The protocol-required

Table 11.1-1: Data Collection Schedule

	Baseline/ Procedure/ Discharge	Follow-up Visits			
		30 Days (±7 Days)[b]	6 Months (±30 Days)[b]	12 Months (±30 Days)[b]	2 Years (±30 Days)[b]

follow-ups may be performed via telephone interview or an office visit within the applicable follow-up window. Beyond the 12-month follow-up, follow-up will be limited to the Safety Population (e.g., those study subjects who received a study stent). Subjects who are enrolled but who do not receive a study stent will be followed for 12 months only.

c: Height and weight should be documented in the eCRF if available in the subject medical record

d: Preprocedure cardiac enzymes can be drawn from the sheath at the time of sheath insertion. If cardiac enzymes are drawn preprocedure, the two results drawn closest to the procedure time should be recorded in the eCRF.

e: In subjects with Non-STEMI, 2 cardiac enzyme draws (as per standard of care) should be obtained prior to the index procedure if possible

f: Two cardiac enzyme draws must be obtained at intervals per standard of care within 24 hours after the index procedure. The first draw should be performed 6-12 hours postprocedure and the second draw should be performed 18-24 hours postprocedure. If the subject is discharged prior to 18 hours postprocedure, the second draw should be obtained at the time of discharge (it is recommended that in these cases the second draw occur no earlier than 16 hours postprocedure).

g: ADEs, SAEs, SADEs, UADEs, USADEs, CEC events, and device deficiencies will be monitored and reported to BSC from the time of enrollment through the 12-month follow-up for all subjects enrolled (regardless of whether a study stent was received) and beyond the 12-month follow-up through the 2-year follow-up for the Safety Population (e.g., those study subjects who received a study stent).

Abbreviations: ADE=adverse device effect; BSC=Boston Scientific Corporation; PCI=percutaneous coronary intervention; SADE=serious adverse device effect; SAE=serious adverse events; UADE=unanticipated adverse device effect; USADE=unanticipated serious adverse device effect

11.2. *Study Candidate Screening*

A Screening Log will be maintained to document selected information about subjects who fail to meet the EVOLVE 48 trial eligibility criteria, including the reason for screen failure.

11.3. *Informed Consent*

Before any study specific tests or procedures are performed, subjects who meet eligibility criteria will be asked to sign the IRB/IEC-approved study ICF. Subjects must be given ample time to review the ICF and have questions answered before signing.

In the US, subjects must sign the ICF prior to the procedure. Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, cardiac catheterization may demonstrate that the subject is not a suitable candidate for the trial.

In Europe and New Zealand, the subject must sign the ICF within 12 hours post procedure.

Refer to section 10.1 for definition of point of enrollment.

11.4. *Baseline/ Procedure / Discharge*

The following data must be collected:

- Confirmation of clinical eligibility criteria
- Demographics including age, gender, and race and ethnicity (unless restricted by local laws)
- Medical history (general medical, cardiac, neurological, renal and peripheral history), including but not limited to, the following
  - Diabetes mellitus status
  - Current angina status
  - Height and Weight
- Current antiplatelet medications
- For the most recent previous PCI procedure, vessel treated, site treated, and type of procedure performed
- Pre-procedure cardiac enzymes should be recorded if drawn based on the standard of care. The one or two (if two enzyme draws are performed) results drawn closest to the start of the procedure should be recorded in the eCRF

Note: Preprocedure cardiac enzymes can be drawn from the sheath at the time of sheath insertion.

Note: It is recommended that the data listed above are obtained within 14 days prior to the procedure.

Note: In subjects with Non-STEMI, 2 cardiac enzyme draws (as per standard of care) should be obtained prior to the index procedure if possible.

Note: While Troponin is the preferred cardiac enzyme, it is recommended that the same type of cardiac enzymes be analyzed prior to the index procedure and postprocedure for a given index hospitalization (i.e., not switching from CK-MB to troponin or vice versa).

11.5. *Required Concomitant Medications*

Protocol-required concomitant medications must be reported in the electronic case report form (eCRF) from the time of baseline through the 2-year follow-up. Information pertaining to the use of antiplatelet medications including dose changes, medication interruptions, and medication cessation, must be documented. Additional concomitant medications may be prescribed at the discretion of the treating physician according to standard of care.

11.5.1. **Loading Dose (P2Y12 inhibitor)**

- For subjects who have been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who have not been taking a P2Y12 inhibitor for ≥ 72 hours at the time of the index procedure, a loading dose is recommended. It is recommended that the loading

dose be administered prior to the index procedure or not more than 2 hours after the index procedure. The following loading doses are recommended:

- Clopidogrel: A peri-procedural loading dose of ≥ 300 mg is recommended.
- Prasugrel: A peri-procedural loading dose of 60 mg is recommended.
- Ticagrelor: A peri-procedural loading dose of 180 mg is recommended.

11.5.2. **Loading Dose (Aspirin)**

- For subjects who have been taking aspirin daily for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who have not been taking aspirin daily for ≥ 72 hours at the time of the index procedure, a loading dose of aspirin is recommended prior to the index procedure. The dosage of the loading dose is at the discretion of the Investigator. It is recommended that the loading dose be administered prior to the index procedure.

11.5.3. **In the Cardiac Catheterization Laboratory**

The subject must be treated with heparin or an alternative antithrombotic (such as bivalirudin or enoxaparin) during the interventional portion of the procedure. If heparin is used, maintenance of an activated clotting time (ACT) >250 seconds throughout the interventional portion of the procedure is recommended. If enoxaparin or bivalirudin is used for procedural anticoagulation, monitoring of the anticoagulation level should be performed according to local laboratory practice.

Note: Abciximab, eptifibatide, and tirofiban may be used at the discretion of the Investigator.

To eliminate coronary artery spasm that would interfere with accurate measurement of lumen obstruction due to plaque alone, intracoronary nitroglycerin (NTG) or isosorbide dinitrate (ISDN) should be administered prior to the baseline angiogram. A dose of 100-200 μg of NTG is preferred; however, a 50 μg dose of NTG may be administered at the Investigator's discretion when deemed clinically necessary. Alternatively, if ISDN is administered, a dose of 2-3 mg is recommended.

11.5.4. **Postprocedure**

The treatment described in this section is applicable to subjects who receive a study stent in a target vessel. Subjects who are enrolled but who do not receive a study stent should be treated per standard of care and followed per protocol.

Based on the ACC/AHA/SCAI and ESC guidelines, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor must be prescribed as follows to reduce the risk of thrombosis.

11.5.4.1. $P2Y_{12}$ inhibitor

Subjects must be treated with one of the following P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor). The dose and duration should be based on current guidelines.

- In subjects with stable ischemic heart disease (SIHD) P2Y12 inhibitor therapy should be given for at least 6 months post stent implantation. For subjects at high risk of bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable.
- In subjects with acute coronary syndrome (ACS) P2Y12 inhibitor therapy should be given for at least 12 months. For subjects at high risk of bleeding, discontinuation of P2Y12 inhibitory therapy after 6 months may be reasonable.

11.5.4.2. Aspirin

Subjects must be treated with aspirin for the duration of the trial. The minimum daily maintenance dose of aspirin should be 75–100 mg.

11.5.4.3. Optimal medical therapy

In addition to dual antiplatelet therapy, it is recommended that subjects be treated with optimal medical therapy (including statins and beta blockers) in order to improve outcomes.

11.6. *Cardiac Catheterization*

11.6.1. **Index Procedure**

The start of the index procedure is defined as the time of sheath insertion. If a previously placed sheath is used (i.e., from a separate diagnostic procedure), index procedure start time is defined as the time of guide catheter insertion into sheath for the interventional procedure.

During cardiac catheterization, the following procedures and assessments must be completed.

- Angiography should be performed according to the Angiographic Core Laboratory procedure guidelines.
- Confirm angiographic eligibility criteria of lesion(s).
- Pre-dilate/pretreat the target lesion and non-target lesion (if applicable)

Note: Balloon catheter predilatation/pretreatment is **required** for the target lesion and non-target lesion (if applicable)**.** The target lesion must be successfully predilated/pretreated in order for the subject to be eligible for enrollment. Unsuccessful predilatation/pretreatment of the target lesion excludes the subject from enrollment in this trial. The subject should be treated per local standard of care, but must not be enrolled or receive a study stent

If a non-target lesion is to be treated, it should be treated prior to the target lesion and should be deemed an angiographic success. Following the successful treatment of the non-target lesion, predilation of the target lesion may then be performed.

Note: Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than NHLBI type C.

Note: Per AE6 (**Table 9.3-1**), the planned treatment should not result in overlap of the study stent with a previously placed stent.

- If stenting is required in a bailout situation within the target vessel, it is recommended the stent be a SYNERGY stent or another everolimus eluting stent.
    - Bailout typically refers to a peri-stent dissection but can also include a vessel complication at the ostium or along the course of the major coronary artery used to access the target lesion.
    - The decision of whether to treat in a bailout situation is at the discretion of the Interventionalist.
    - In cases of bailout, the stent used should be documented in the eCRF.

11.6.1.1. Stent Placement

Refer to the DFU for detailed instructions about preparation and placement of the SYNERGY stent.

11.6.2. Post Stent Deployment Procedures

After stent placement, the Investigator should ensure that the stent is in full contact with the arterial wall. In order to achieve full contact, postdilatation may be performed at the discretion of the Investigator using the stent delivery system balloon or other balloon catheter.

Peri-stent dissections should be treated conservatively, with low pressure prolonged balloon inflation, or with additional stent implantation per standard practice. Haziness, lucency, or filling defects within or adjacent to the stent, and angiographic complications such as distal thromboemboli or no reflow, should also be treated per standard practice. All angiographic complications that occur should be documented by angiography and submitted to the Angiographic Core Laboratory for analysis.

To eliminate coronary artery spasm that would interfere with accurate measurement of lumen obstruction due to plaque alone, NTG or ISDN should be administered prior to the final angiogram. A dose of at least 100 μg of NTG is preferred; however, a 50 μg dose of NTG may be administered at the Investigator's discretion when deemed clinically necessary. Alternatively, if ISDN is administered, a dose of 2-3 mg is recommended.

11.7. *End of the Index Procedure*

The end of the index procedure is defined as the time the guiding catheter was removed (post final angiography). The introducer(s) sheaths should be removed as per standard local practice. The following procedures must be completed:

- Document procedural, target lesion, non-target lesion (if applicable), pre-dilatation, post-dilatation (if applicable), and study stent information on the appropriate eCRFs.
- Record antithrombotic medications
- Complete AE assessment and collect source documents as described in Section 20

- Finalize angiographic procedure film and related required documentation to submit to the Core Laboratory per instructions set in the Manual of Operations

11.8. *Postprocedure/Prehospital Discharge*

The subject may be discharged from the hospital when clinically stable at the Investigator's discretion but preferably not less than 18 hours after the index procedure. The following assessments must be completed post index procedure.

- Angina assessment
- Cardiac enzymes

  Two cardiac enzyme draws must be obtained at intervals per standard of care within 24 hours after the index procedure. The first draw should be performed 6-12 hours postprocedure and the second draw should be performed 18-24 hours postprocedure.

  Note: If the subject is discharged prior to 18 hours postprocedure, the second draw should be obtained at the time of discharge (it is recommended that in these cases the second draw occur no earlier than 16 hours postprocedure).

- Record antiplatelet medications
- Complete AE assessment and collect source documents as described in Section 20

It is important that trial site personnel review the trial requirements with the subject to maximize compliance with the follow-up schedule and required medication regimen. It is also important that trial site personnel instruct subjects to return for follow-up assessments according to the trial event schedule in

Table 11.1-1. Study staff should establish a date for the follow-up telephone call with the subject and if possible, schedule the visit at the time of hospital discharge.

11.9. *Angiography*

All subjects will undergo angiographic assessment during the index procedure per standard of care. Subjects requiring reintervention for the target vessel during the 2-year follow-up period will undergo angiographic assessment at the time of reintervention as standard of care. Angiographic data and images collected during the index procedure and during any reinterventions of a target vessel during the 2-year follow-up period must be forwarded to the Angiographic Core Laboratory for analysis. Angiograms performed at outside institutions should also be sent to the Core Laboratory.

Angiograms will be centrally assessed by the Angiographic Core Laboratory, for qualitative and quantitative analysis including longitudinal stent deformation.

11.10. *Follow-Up*

All enrolled subjects who receive a study stent will be evaluated through hospital discharge and at 30 days, 6 months, 12 months and 2 years after the index procedure. Subjects who are enrolled but who do not receive a study stent will be followed for 12 months only.

All protocol-required follow-up assessments must be conducted with direct contact with the subjects either in person or by telephone interview. At the time of each protocol required follow-up, study site personnel should answer any study related questions the subject may have in addition to completing the required protocol assessments. In the absence of cardiac symptoms, routine follow-up, cardiac procedures, and tests are left to the discretion of the Investigator.

During the 2 year follow-up period, if the subject experiences an event, it must be assessed and documented as described in Section 20. If the subject experiences new or recurrent cardiac symptoms during the trial, a more detailed evaluation (including repeat angiography) may be performed at the discretion of the Investigator and treating physicians.

If the subject undergoes repeat catheterization, the circumstances and outcome of the event must be assessed and documented as described in Section 20. If the repeat catheterization results in reintervention of the target vessel(s), angiographic data and images must be sent to the Angiographic Core Laboratory.

Subjects requiring reintervention should be treated according to the Investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment (if appropriate) and must not receive an investigational study stent for retreatment. Prior to initiating an angiogram, the results of the subjects' clinical status and functional testing should be documented. Prior to conducting the angiogram, indication(s) for the angiogram must be documented.

11.10.1. **30-Day Follow-up (30±7 Days)**

All enrolled subjects must be evaluated 30 days after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 30 day follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 20
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

11.10.2. **6-Month Follow-up (180±30 Days)**

All enrolled subjects must be evaluated 6 months after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 6 month follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 20
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

11.10.3. **12-Month Follow-up (365±30 Days)**

All enrolled subjects must be evaluated 12 months after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 12 month follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 20
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

11.10.4. **2-Year Follow-up (730±30 Days)**

All enrolled subjects who receive a study stent must be at evaluated 2 years after the index procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 2 year follow-up, the following assessments must be completed.

- Angina assessment
- AE assessment and source document collection as described in Section 20
- Current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions, and medication cessation must be documented.

11.10.5. **Additional Interim Follow-up**

Additional interim follow-up visits may be conducted at the Investigator's discretion. Clinical study-specific medical care will terminate upon completion or termination of the subject's participation in the study.

11.10.6. **Missed or Late Visits**

A subject will be considered lost to follow-up after the subject misses the first (12 m) and final (2 year) follow-up visit. A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject for each missed follow-up visit and this information documented in the source.

Missed or late visits will be recorded as Protocol Deviations.

11.11. ***Study Completion***

Enrolled subjects that received a SYNERGY 48 mm stent will be followed for 2 years after the index procedure.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. **Primary Endpoint**

The primary endpoint is the 12 month (365 days) TLF expressed as the proportion of subjects who experience TLF within 365 days after the index procedure among all subjects who either experience TLF within 365 days after the index procedure or are followed for at least 335 days after the index procedure.

12.1.1.1. Hypotheses

The 12-month TLF rate for SYNERGY subjects with 48 mm is less than the performance goal (PG) of 19.5%.

12.1.1.2. Sample Size

- The expected 12-month TLF rate for SYNERGY = 9.2%; estimated by the observed rate (6.6%) for SYNERGY in EVOLVE II RCT and a 40% relative increase for TLF due to longer lesion length (assuming a relative 20% increase in rates for every 10 mm increase in mean lesion length) with an expected mean lesion length of 20 mm longer than the one observed in EVOLVE II RCT (mean lesion length of 16 mm for SYNERGY arm), i.e. 6.6% * (1 + 20%* 2) = 9.2%
- The Performance Goal = 19.5%; based on EVOLVE II-like patients with lesion length greater than 34 mm and less than or equal to 44 mm from PROMUS Element Plus US Post-Approval Study and PE-Prove Study. The pooled historical 12 month TVF rate related to study stent from these 2 studies (6.7% (3/45) and 0% (0/12), respectively) is 5.3% (3/57) with the corresponding exact binominal one-sided 95% upper CI of 13%. The expected control rate for these long lesion patients is chosen to be the exact binomial one-sided 95% upper CI of 13% of the pooled historical rate accounting for the lack of systematic post-procedural enzyme collection in the Post-Approval studies, small sample size and the event rate variability between studies. The PG is set to be 19.5% (expected control rate 13% + delta, where delta is chosen to be relative 50% of the expected control rate of 13% = 6.5%)
- Test significance level (α) = 0.05 (1-sided)
- Power ($1-\beta$) $\geq$ 0.80
- N = 95 evaluable patients
- Expected attrition rate = 5%
- N=100 enrolled patients
- The worst observed rate allowable for meeting the PG of 19.5% is 12% (12/100)

12.1.1.3. Statistical Methods

A one-group Clopper-Pearson exact test will be used to test whether the 12‑month TLF rate for SYNERGY is less than the PG.

12.2. *General Statistical Methods*

12.2.1. **Analysis Sets**

The primary endpoint will be analyzed on an ITT basis and on a per-protocol basis. For the ITT analysis, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether the study stent was implanted. For the per-protocol analysis, only enrolled subjects who received a 48 mm SYNERGY stent in the target lesion will be included in the analysis sample.

A conclusion of the 48 mm SYNERGY stent meeting the PG with respect to the 12-month TLF rate is tested successfully if the *P* value from the one-sided Clopper-Pearson test is <0.05 in both the per-protocol and ITT populations. This corresponds to the one-sided 95% upper confidence bound on the observed 12-month TLF rate from SYNERGY being less than the PG.

12.2.2. **Control of Systematic Error/Bias**

Selection of subjects will be made from the Investigator's usual subject load. All subjects meeting the inclusion/exclusion criteria and having signed the ICF will be eligible to enroll in the trial. Consecutively eligible subjects should be enrolled into the study to minimize selection bias. In determining subject eligibility for the study, the investigator's assessment of angiographic parameters before stent placement will be used. However, the Angiographic Core Laboratory will independently analyze the angiograms and the data obtained from the core lab will be used for analyses in order to control for inter-observer variability. An independent CEC composed of expert cardiologists will adjudicate all reported events of death, MI, TVR, and stent thrombosis.

12.2.3. **Number of Subjects per Investigative Site**

Investigative sites are recommended to enroll preferably a minimum of 6 subjects but no more than 20 subjects (20% of the total number of subjects) in the trial.

12.3. *Data Analyses*

Baseline data will be summarized, post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, and n, minimum, maximum) and frequency tables or proportions for discrete variables. Estimates of primary and other endpoints will be reported and their 95% confidence intervals will be presented. No formal statistical testing will be done for other endpoints.

12.3.1. **Other Endpoints/Measurements**

Clinical event rates will be summarized using proportions while continuous data will be summarized by presenting means, standard deviations, sample sizes, minimums, and maximums.

Kaplan-Meier time-to-event plots will be constructed for clinical events. The analysis of stent thrombosis will focus on all events in the "possible", "probable", "definite", and "definite or probable" categories, according to ARC definitions. Rates of serious adverse events (SAEs) and AEs will be reported.

No formal tests of hypotheses are proposed for additional endpoints.

12.3.2. **Interim Analyses**

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility.

12.3.3. **Subgroup Analyses**

Primary endpoint of 12 month TLF and its clinical components will be summarized by gender (male and female). Given limited sample size, no other subgroup analyses will be performed.

12.3.4. **Justification of Pooling**

In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects in the study but no more than the largest enrolling center.

12.3.5. **Multivariable Analyses**

Univariate and multivariate analyses may be performed to assess the effect of potential predictors on the primary endpoint of 12 month TLF using Logistic regression. Analyses may also be performed for pre-specified clinical endpoints, if feasible; liner regression may be used for continuous outcomes and Cox proportional hazards regression may be used to assess the effects of possible predictors in a time-to-event manner.

Variables from the following categories will be considered as possible predictors: demographics, medical history, coronary artery disease risk factors, procedural characteristics, baseline angiographic measurements, and medication used during study procedure.

12.3.6. **Other Analyses**

Adjustments for missing data will be performed if deemed necessary to eliminate or minimize bias and will be described completely. Statistical models that account for censored data will be employed in appropriate circumstances, e.g., for time-to-event outcomes. Sensitivity analyses, including a tipping-point analysis for the primary endpoint, may be conducted to assess the impact of different assumptions about the missing data on interpretation of the results. Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid.

12.3.7. **Changes to Planned Analyses**

Any changes to the planned statistical analyses made prior to performing the primary endpoint analysis will be documented in an amended Statistical Analysis Plan approved prior to performing the analysis. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the

data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

The EVOLVE 48 trial will use an Angiographic Core Laboratory for analysis of angiography data. Results from the angiographic Core Laboratory will be entered or uploaded into the EDC system and will only be available to BSC.

All subjects will undergo angiographic assessment during the index procedure. Angiographic follow-up is not required; however, subjects requiring reintervention for the target vessel during the 2-year follow-up period will undergo angiographic assessment at the time of reintervention as standard of care.

Angiographic data, images, and technician's worksheets collected during the index procedure and during reinterventions for the target vessel(s) during the 2-year follow-up period (if applicable) must be forwarded to the Angiographic Core Laboratory for analysis. Angiographic data and images for reintervention for vessels not treated during the study index procedure should not be sent to the Angiographic Core Laboratory.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC where applicable, of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days. All

deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including but not limited to, IRB/EC/FDA notification, site re-training, or site discontinuation/ termination) will be put into place by the sponsor.

16. Device Accountability

16.1. *Region – US*

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices, if applicable.

16.2. *Region – Outside US*

In regions where the SYNERGY 48 mm is commercially available the devices for subjects enrolled in the study will be selected from the sites commercial inventory. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the devices, which shall include the following

- Identification of each device (lot number)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the device was returned/explanted from subject, if applicable
- Date of return of malfunctioning devices, if applicable.

Written procedures may be required by national regulations.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national

regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.

- Investigators in the US must maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that a plan of oversight is documented when multiple locations (satellite sites) are overseen by one Principal Investigator.
- Inform the Sponsor of any site location changes, additions to, or deletions from sites where study subjects are seen or treated; inform IRB/EC and update Informed Consent Form accordingly.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. **Delegation of Responsibility**

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment (if applicable). Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

18. Monitoring

Monitoring will be performed during the study, according to the Monitoring Plan, to assess continued compliance with the current, approved protocol/amendment (s) and applicable regulations. In addition, the clinical research monitor verifies that informed consent is obtained from all enrolled study subjects, study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. Monitoring strategies will be tailored to risks, and will be focused on critical processes and critical data. Monitoring activities will be adjusted based on the issues and risks identified throughout the study. Pre-defined thresholds for protocol deviation and compliance once met or exceeded, can also trigger increased monitoring frequency and/or the implementation of corrective action plans at clinical sites. Source documents include, at a minimum but not limited to, the ICF; subject medical records, including nursing records and catheterization laboratory records; diagnostic imaging records; laboratory results; and reports of SAEs and device accountability logs. Data documented in the eCRF relevant to device deficiencies, relationship of AE to study device(s), index procedure, and antiplatelet medication; and anticipatedness assessment of ADEs, may be considered source data for the study.

A risk-based approach to source data verification will be implemented as described in the Monitoring Plan. The monitoring plan for EVOLVE 48 will include source data verification of critical data for a sampling of subjects enrolled and review of 100% of ICFs for all subjects.

The Principal Investigator/institution guarantees direct access to original source documents (electronic or paper) by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. Photocopies of original source documents related to SAEs (from either the study site or a non-study institution, if applicable) must also be made available for submission to the BSC Safety Office as described in Section 20.The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1. *Risks Associated with the Implantation of Coronary Stents*

Potential AEs (in alphabetical order) which may be associated with the implantation of a coronary stent or the associated cardiac catheterization are listed below:

- Abrupt stent closure
- Acute MI

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

19.2. *Risks Associated with Everolimus*

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the US 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 US 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 (38) .The amount of drug that circulates in the bloodstream following implantation of SYNERGY stent is significantly lower than that obtained with oral doses.

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia

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

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

19.3. *Anticipated Adverse Device Effects*

The anticipated adverse device effects (ADE) have been identified and are listed in section 19.1 and 19.2.

19.4. *Risks Associated with the Study Device(s)*

The SYNERGY stent releases everolimus via a bioabsorbable PLGA polymer. This polymer formulation has previously been used to achieve controlled release of everolimus in the SYNERGY FHU stent in the EVOLVE trial. The SYNERGY stent has also been used in the EVOLVE II program, for which primary endpoint results and follow up through 3 years are available. Several clinical trials have demonstrated the safety and performance of other drug-eluting stents that use similar polymer formulations to control the release of pharmaceutical agents from a coronary stent (28-30). These clinical trials, in combination with the EVOLVE trials, suggest that the risk associated with the SYNERGY stent is comparable to other drug-eluting coronary stents. When considering the incremental risk of using a 48 mm stent versus a shorter stent, it is conceivable that it might be more challenging to deliver a 48 mm stent than a shorter stent. If it is not possible to deliver a 48 mm stent – use of two overlapping stents is a bailout option. Another consideration is the vessel tapering which could potentially be more pronounced in a longer stent. However, vessel tapering is expected to affect the post-dilation strategy more than stent selection. The overexpansion capabilities of SYNERGY provide adequate margin for the anticipated variation in vessel size.

19.5. *Sex-Specific Risks Associated with the Study Device(s)*

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

19.6. *Risks Associated with Participation in the Clinical Study*

In addition to the aforementioned risks associated with the implantation of coronary stents and the use of everolimus, the use of dual antiplatelet therapy after stent implantation may increase the risk of bleeding. There may be additional risks linked to the procedure which are unforeseen at this time.

19.7. *Possible Interactions with Concomitant Medical Treatments*

The following describes known drug interactions for orally administered everolimus at significantly higher doses than are present on the PROMUS Element Plus and SYNERGY stents. Interactions observed at these higher doses may not be relevant to the PROMUS Element Plus and SYNERGY stents.

When taken orally, everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that affect these pathways. Concurrent treatment with strong CYP3A4 inhibitors and inducers is not recommended unless the benefits outweigh the risk. Inhibitors of P glycoprotein may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. In vitro, everolimus was a competitive inhibitor of CYP3A4 and of cytochrome P4502D6 (CYP2D6), potentially increasing the concentrations of drugs eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index (42).

Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine. Formal drug interaction studies have not been performed with the SYNERGY stent. Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the SYNERGY stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the following drugs or substances.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers [verapamil and

diltiazem), aprepitant, atazanavir, nefazodone, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir, and telithromycin)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, efavirenz, nevirapine, and dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- PgP inhibitors (digoxin, cyclosporine)
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit/grapefruit juice

19.8. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

19.9. *Anticipated Benefits*

Anticipated benefits include the effective treatment of coronary artery stenosis and improvement in the symptoms of coronary artery disease. Subjects who receive the SYNERGY stent may have better vessel healing, a lower risk of stent thrombosis, and less of a need for prolonged dual antiplatelet therapy. Regarding specifically the use of a long stent, clinical data form the TAXUS ATLAS Long Lesion trial suggests a benefit of treatment with a single long stent versus multiple overlapping stents (31). It is also conceivable that the use of one versus two overlapping stents potentially decreases contrast use, exposure to irradiation and procedure time. However, given there are no clinical data on the SYNERGY 48 mm stent these potential benefits may or may not actually be present

19.10. *Risk to Benefit Rationale*

The 48 mm SYNERGY stent is expected to be suitable for its intended purpose. There are no new patient harms associated with the use of a 48 mm SYNERGY stent versus using a shorter SYNERGY stent. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate Directions for Use. Evaluation of the risks and benefits that are expected to be associated with use of the 48 mm SYNERGY stent demonstrate that when used under the conditions intended, the benefits associated with use of the 48 mm SYNERGY stent should outweigh the risks.

20. Safety Reporting

20.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All serious adverse events (SAE)
- All CEC events inclusive of death, MI*, TVR and stent thrombosis
- All Adverse Device Effects (ADE)
- All SYNERGY 48 mm Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

* MI should be reported per protocol definition. If pre-procedure cardiac enzymes were not drawn, but the event otherwise meets the protocol definition of MI, the event should be reported as an MI for CEC adjudication.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or events occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and event AEs must be reported if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

20.2. *Definitions and Classification*

Adverse event definitions are provided in Table 20.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 20.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization , or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree

Table 20.2-1: Safety Definitions

Term	Definition
Ref: 21 CFR Part 812	of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

20.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 20.3-1:

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error;

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.4-1.

Table 20.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline**
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event*	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency CRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Within 10 business days after becoming aware of the information • ADEs reporting required through end of study

***** All CEC events must be reported using the timeframe for SAE, regardless of whether they meet serious criteria

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

20.5. *Boston Scientific Device Deficiencies*

All SYNERGY 48 mm device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the MOP. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events; they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an adverse event results from a device failure or malfunction, the AE should be recorded as an adverse event on the appropriate eCRF if it meets the protocol-specified definition of a reportable event.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

20.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

Boston Scientific Corporation will notify all participating study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting AE and device deficiencies information to all participating investigators, IRBs/IECs, and regulatory authorities as applicable according to local reporting requirements.

Boston Scientific Corporation, Investigator, or Site must notify the IRB/IEC of any UADEs, USADEs, SADEs, SAEs, device deficiencies, and other CEC events as applicable according to local reporting requirements (refer to Section 22 for information pertaining to the CEC and CEC Events). A copy of the Investigator's reports and other relevant reports (if applicable) to the IRB/IEC must be provided to BSC in accordance with local requirements.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, the presence of, addition, or deletion of satellite sites or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, cardiac catheterization may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained to document select information about candidates who fail to meet the EVOLVE 48trial eligibility criteria, including, but not limited to, the reason for screen failure.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, BSC processes will provide accelerated evaluation of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the sites and Angiographic Core Laboratory. During regularly scheduled monitoring visits, the clinical research monitors will support the dynamic reporting process through their review of source document information.

22.2. *Clinical Events Committee*

The Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise who review and adjudicate important clinical endpoints and relevant AEs reported by study Investigators.

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported cases of stent thrombosis, TVR, MI (Q-wave and non–Q-wave), and death.

Committee membership will include practitioners of cardiology and cardiovascular interventional therapy, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

23. Suspension or Termination

23.1. *Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1. **Criteria for Premature Termination of the Study**

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or IRB/ EC in the EVOLVE 48 Study may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The

IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled, if enrollment is significantly slower than expected, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed per protocol as defined in Section 11. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.

- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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Abbreviations and Definitions

25.1. *Abbreviations*

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
AHA	American Heart Association
ARC	Academic Research Consortium
BSC	Boston Scientific Corporation
BMS	bare metal stent
CABG	coronary artery bypass graft
CBC	complete blood count
CEC	Clinical Events Committee

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRO	Contract research organization
eCRF	electronic case report form
CVA	cerebrovascular accident
DES	drug-eluting stent
DFU	Directions for Use
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FHU	First Human Use
FFR	fractional flow reserve
GCP	Good Clinical Practices
GI	gastrointestinal
GUSTO	Global Strategies for Opening Occluded Coronary Arteries
IABP	intra-aortic balloon pump
IC	Intercontinental
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISDN	isosorbide dinitrate
ISO	International Standards Organization
ITT	intention to treat
IVRS	interactive voice response system
IWRS	Interactive web response system
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LCX	left circumflex coronary artery
LL	long lesion
MACE	major adverse cardiac event

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
MI	myocardial infarction
MLD	minimum lumen diameter
NHLBI	National Heart, Lung, and Blood Institute
NTG	Nitroglycerin
OUS	Outside the United States
PCI	percutaneous coronary intervention
PG	Performance Goal
PK	pharmacokinetics
PLGA	poly(DL-lactide-co-glycolide)
POBA	Plain Old Balloon Angioplasty
QCA	quantitative coronary angiography
RCA	right coronary artery
RVD	reference vessel diameter
SADE	serious adverse device effect
SAE	serious adverse event
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST elevation myocardial infarction
SV	Small vessel
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	target lesion failure
TLR	target lesion revascularization
TVF	target vessel failure
TVR	target vessel revascularization
UADE	unanticipated adverse device effect
ULN	upper limit of normal
URL	upper reference limit
US	United States
WBC	white blood cell
WH	Workhorse

25.2. *Definitions*

Terms are defined below.

ABRUPT CLOSURE

Abrupt closure is the occurrence of new severely reduced flow (TIMI grade 0 or 1) within the target vessel that persists and requires bailout, including emergency surgery, or results in MI or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" due to microvascular flow limitation in which the epicardial artery is patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the assigned treatment reversed the closure.

Sub-abrupt closure is an abrupt closure that occurs after the target procedure is completed and the subject has left the catheterization laboratory and before hospital discharge.

Threatened abrupt closure is a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3)*

Adverse event related to the use of an investigational medical device

> NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
>
> NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.

ADVERSE EVENT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational medical device or comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.

ADVERSE EVENT RELATIONSHIP TERMS

Adverse Event Relationship terms are detailed in section 20.3-1.

ANGIOGRAPHIC SUCCESS

Angiographic success is a mean lesion diameter stenosis < 50% (< 30% for stents) in 2 near-orthogonal projections with TIMI 3flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI

ANNUAL FOLLOW-UPS

Annual follow-ups are those that occur annually through 2 years after the index procedure. The timing of annual follow-ups is calculated based on one calendar year equaling 365 days.

The follow-up window is 30 days. Therefore, the 1-year and 2-year follow-ups should occur 365±30 days and 730±30 days after the index procedure, respectively.

ANTICIPATED EVENT

Event that is previously identified in the Protocol, ICF, or DFU.

ARRHYTHMIA

An arrhythmia is any variation from the normal rhythm of the heart, including sinus arrhythmia, premature beats, heart block, atrial or ventricular fibrillation, atrial or ventricular flutter, and atrial or ventricular tachycardia.

ARTERIOVENOUS FISTULA

An arteriovenous fistula is an abnormal passage or communication between an artery and a vein. It may result from injury or it may occur as a congenital abnormality.

BAILOUT

- Bailout typically refers to a peristent dissection but can also include a vessel complication at the ostium or along the course of the major coronary artery used to access the target lesion.
- The decision of whether to treat in a bailout situation is at the discretion of the interventionalist.

BIFURCATION LESION

A bifurcation lesion is a lesion associated with the area where a branch vessel >2.0 mm in diameter by visual estimate originates.

BINARY RESTENOSIS

Binary restenosis is a diameter stenosis >50% at the previously treated lesion site, including the original treated area and the adjacent proximal and distal QCA analysis segment.

BLEEDING CLASSIFICATIONS (*Ref: GUSTO*)

- Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise
- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity

- Class I: New onset, severe or accelerated angina. Subjects with angina of less than 2 months duration, severe or occurring 3 or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no pain at rest in the last 2 months.

- Class II: Angina at rest, subacute. Subjects with 1 or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.
- Class III: Angina at rest, acute. Subjects with 1 or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances

- Class A: Secondary unstable angina. A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia (e.g., anemia, fever, infection, hypotension, tachyarrhythmia, thyrotoxicosis, and hypoxemia secondary to respiratory failure).
- Class B: Primary unstable angina.
- Class C: Postinfarction unstable angina (within 2 weeks of documented MI).

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION

- Class 1: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
- Class 2: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or any only during the first hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
- Class 3: Marked limitations of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
- Class 4: Inability to carry on any physical activity without discomfort; angina syndrome may be present at rest.

CARDIAC TAMPONADE

Cardiac tamponade is an acute compression of the heart due to effusion of the fluid into the pericardium, or the collection of blood in the pericardium, from rupture of the heart or penetrating trauma.

CARDIOGENIC SHOCK

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic blood pressure <80 mmHg and/or a central filling pressure >20 mmHg, or a cardiac index <1.8 liters/min/m^2 where there is evidence of insufficient end organ profusion. Shock is also considered present if intravenous inotropes and/or intra-aortic balloon pump (IABP) are needed to maintain a systolic blood pressure >80 mmHg and a cardiac index >1.8 liters/minute/m^2.

CREATINE KINASE-MYOGLOBIN BAND

Creatine kinase-myoglobin band (CK-MB) is an isoenzyme of creatine kinase (CK) with a distinct molecular structure specific as an indicator of myocardial cell injury. It is used to evaluate possible causes of chest pain, to detect and diagnose acute MI and re-infarction, and to monitor the severity of myocardial ischemia.

CLINICAL EVENTS COMMITTEE

A CEC is an independent group of individuals with pertinent expertise that review and adjudicate important endpoints and relevant AEs reported by study investigators.

CLINICAL EVENTS COMMITTEE EVENT

The CEC will adjudicate all reported cases of stent thrombosis, TVR, MI (Q-wave and non–Q-wave), and death (to ensure appropriate classification of death as cardiac or non-cardiac). A case adjudicated by the CEC is considered to be a CEC event.

CLINICAL PROCEDURAL SUCCESS (VISUAL ESTIMATE)

Clinical procedural success is postprocedure diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow in the target lesion, as visually assessed by the physician, without the occurrence of in-hospital MI, TVR, or cardiac death.

COMPLICATION (ANGIOGRAPHIC OR CLINICAL)

A complication (angiographic or clinical) is an undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to, perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, non-fatal MI, elevated CK Total, prolonged angina, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational device.

CONGESTIVE HEART FAILURE

Congestive heart failure is an inadequacy of the heart such that it fails to maintain adequate circulation of blood, so that congestion and edema develop in the tissues. Clinical syndrome is characterized by shortness of breath, non-pitting edema, enlargement of the liver, engorged neck veins, and pulmonary rales.

CORONARY ANEURYSM

A coronary aneurysm is a pathologic dilatation of a segment of a blood vessel involving all three layers of the vessel wall ≥1.5× the RVD.

CORONARY ARTERY SPASM

Coronary artery spasm, or coronary vasospasm, is a spasm of a coronary artery, resulting in a decrease in lumen diameter. It may occur distal to the treatment site and is generally reversed with intracoronary administration of NTG or with adjunct balloon dilatation.

DEATH

Death is categorized as cardiac or non-cardiac.

Cardiac death is defined as death due to any of the following.

- Acute MI
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- CVA through hospital discharge or CVA suspected of being related to the procedure

- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
- Any death in which a cardiac cause cannot be excluded

Non-cardiac death is defined as a death not due to cardiac causes as defined above.

DEVICE DEFICIENCY (*Ref: ISO 14155 and MEDDEV 2.7/3*)

A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

DISSECTION, NHLBI CLASSIFICATION

- Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material
- Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
- Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
- Type D: Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow
- Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen
- Type F: Filling defect accompanied by total coronary occlusion

DIABETES MELLITUS

Subjects will be categorized as having diabetes mellitus if medical treatment (oral or injection) is required for control of blood glucose levels.

DISTAL EMBOLIZATION

Distal embolization is migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

EMERGENCY BYPASS SURGERY

Emergency bypass surgery is CABG surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

EPICARDIAL VESSEL

Epicardial vessels include the LAD and its branches, the LCX and its branches, and the RCA and its branches.

HYPERTENSION

Hypertension is persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140 mmHg systolic and 90 mmHg diastolic to as high as 220 mmHg systolic and 110 mmHg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

HYPOTENSION

Sustained hypotension is a systolic blood pressure less than 80 mmHg lasting more than 30 minutes or requiring intervention (e.g., pacing, IABP, intravenous vasopressors, to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.

INDEX PROCEDURE START TIME

Index procedure start time is defined as the time of sheath insertion. If a previously placed sheath is used (i.e., from an earlier diagnostic procedure), index procedure start time is defined as the time of guide catheter insertion into sheath for the interventional procedure.

INDEX PROCEDURE END TIME

Index procedure end time is defined as the time the guide catheter is removed after the final angiography.

INTIMAL FLAP

An intimal flap is an extension of the vessel wall into the arterial lumen.

LEFT MAIN DISEASE

Left main disease is a significant lesion in the left main coronary artery of at least 50% diameter stenosis. A protected left main artery means left main with a functioning graft, either venous or arterial, placed to any of the branches of the left main. This is usually the LAD or CX, but could also include one of the branches of those vessels. Having a stent in the left main coronary artery does not in itself constitute a protected left main.

LESION CHARACTERISTICS (ACC/AHA CLASSIFICATION)

- Type A lesions: Minimally complex, length <10 mm, concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.
- Type B lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewire, and some thrombus present.
- Type C lesions: Severely complex, diffuse (length ≥20 mm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION LENGTH

Lesion length is measured as distance from the proximal to the distal shoulder in the view that demonstrates the stenosis in its most elongated projection. Lesion length is classified as discrete (<10 mm), tubular (10-20 mm), or diffuse (>20 mm).

LESION LOCATION

Lesion location is the location of the lesion according to the specific coronary artery (i.e., left main, LAD, LCX, or RCA) or bypass graft, and is specified as proximal, mid, or distal. A standard map will be provided to be used for location descriptions.

Note: In the EVOLVE 48 trial, the ramus will be considered to be a branch of the LCX for purposes of determining eligibility and for determining TVR.

LEUKOPENIA

Leukopenia is a leukocyte count of $<3.0 \times 10^9$/liter for more than 3 days.

MALFUNCTION

A malfunction is a failure of the device to meet performance specifications or otherwise perform as intended.

MULTI-VESSEL DISEASE

Multi-vessel disease refers to the presence of >50% diameter stenosis as measured by caliper method or QCA on-line in 2 or 3 major epicardial coronary vessels or bypassed branches.

MYOCARDIAL INFARCTION

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

Spontaneous MI:

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

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

Percutaneous Coronary Intervention-Related Myocardial Infarction:

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

AND

One of the following:

(i) Symptoms suggestion of myocardial ischemia

(ii) New ischemic ECG changes

(iii) Angiographic findings consistent with a procedural complication

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

Coronary Artery Bypass Grafting-Related Myocardial Infarction:

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

AND

One of the following:

(i) New pathological Q waves or new LBBB

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

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

Myocardial Infarction resulting in death when biomarker values are unavailable:

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

Stent thrombosis- Related Myocardial Infarction:

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

NON-TARGET LESION

A non-target lesion is any lesion treated during the index procedure which is not a target lesion. A maximum of 1 non-target lesion in 1 non-target vessel may be treated with a commercial treatment (e.g., stent, balloon angioplasty, excluding brachytherapy) during the index procedure.

PERFORATION

Perforations are classified as follows:

- Angiographic perforation: Perforation detected by clinical site or Angiographic Core Laboratory at any point during the procedure.
- Clinical perforation: Perforation requiring additional treatment, including efforts to seal the perforation or pericardial drainage, or resulting in significant pericardial effusion, abrupt closure, MI, or death.
- Pericardial hemorrhage/tamponade: Perforation causing tamponade.

PROLONGED ANGINA PECTORIS

Prolonged angina pectoris is angina lasting longer than 1 hour.

PSEUDOANEURYSM

A pseudoaneurysm is an encapsulated hematoma in communication with an artery. It is often difficult to distinguish from an expanding hematoma at the site of arterial puncture. It usually requires surgical repair.

REFERENCE DIAMETER OF NORMAL ARTERY SEGMENT

Reference diameter of the normal artery segment is an angiographic measurement of the artery proximal and/or distal to the lesion intended for angioplasty. This is also referred to as "reference vessel diameter" (RVD).

REPEAT INTERVENTION

Repeat intervention is a PCI or CABG performed after the end of the index procedure. The repeat intervention should be performed to improve blood flow.

RESTENOSED LESION

A restenosed lesion is a previously treated lesion that again has a stenosis.

RESTENOSIS

See Binary Restenosis.

SERIOUS ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SERIOUS ADVERSE EVENT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Adverse event that:

a) Led to death,

- b) Led to serious deterioration in the health of the subject as defined by either:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient hospitalization or prolongation of existing hospitalization , or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.

SOURCE DATA

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a nclinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or ceritifed copies) (ICH E6 (1.51 and 1.52))

SOURCE DOCUMENTS

Original documents, data, and records (ICH E6 (1.51 and 1.52))

STENT THROMBOSIS (*Ref: Academic Research Consortium Definition*) (32)

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guide catheter has been removed and the patient left the catheterization lab.

Timing:

- Acute stent thrombosis*: 0-24 hours after stent implantation
- Subacute stent thrombosis*: >24 hours to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation
- Very late stent thrombosis: >1 year after stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis is 0-30 days.

Stent thrombosis may be defined as:

- Confirmed/definite
- Probable
- Possible

Confirmed/Definite (is considered *either* angiographic confirmed or pathologic confirmed)

Angiographic confirmed stent thrombosis is considered to have occurred if:

- TIMI flow is:

TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of thrombus*

TIMI flow grade 1, 2 or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus*

AND at least one of the following criteria, up to 48 hours, has been fulfilled:

- New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (>2× ULN of CK)

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).

* Intracoronary thrombus

Non-occlusive thrombus: Spheric, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides of within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus: A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

Probable

Clinical definition of probable stent thrombosis is considered to have occurred in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure and MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

Possible

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.

STROKE/CEREBROVASCULAR ACCIDENT

An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction.

Classification:

- Ischemic Stroke: An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke: An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined Stroke: A stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

An event that lasts < 24 hours may be adjudicated as a stroke if the following treatments were used:

- Pharmacologic, i. e., thrombolytic drug administration, or
- Non-pharmacologic, i.e., neurointerventional procedure (*e.g.,* intracranial angioplasty)

SUCCESSFUL PREDILATATION/PRETREATMENT

Successful predilatation/pretreatment refers to dilatation with a balloon catheter of appropriate length and diameter, or pretreatment with directional or rotational coronary atherectomy, laser or cutting/scoring balloon with no greater than 50% residual stenosis and no dissection greater than NHLBI type C.

TARGET LESION

The target lesion is the lesion selected by the Investigator for treatment with a study stent. The target lesion includes the arterial segment treated with the study stent plus the arterial

segment 5 mm proximal and 5 mm distal to the treatment site. The target lesion should meet the angiographic selection criteria.

TARGET LESION FAILURE

Target lesion failure is any ischemia-driven revascularization of the target lesion, MI (Q-wave and non–Q-wave) related to the target vessel, or (cardiac) death. For the purposes of this protocol, if it cannot be determined with certainty whether the MI was related to the target vessel, it will be considered a TLF.

TARGET LESION REVASCULARIZATION

Target lesion revascularization is any ischemia-driven repeat percutaneous intervention, to improve blood flow, of the successfully treated target lesion or bypass surgery of the target vessel with a graft distally to the successfully treated target lesion. A TLR will be considered as ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and there is presence of clinical or functional ischemia which cannot be explained by other coronary or graft lesions. Clinical or functional ischemia is any of the following:

- The subject has a positive functional study corresponding to the area served by the target lesion.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target lesion.

A TLR will be considered as ischemia-driven if the lesion diameter stenosis is ≥70% by QCA even in the absence of clinical or functional ischemia.

TARGET VESSEL

The target vessel is any coronary vessel (e.g., left main coronary artery, LAD, LCX, or RCA) containing a target lesion. Side branches of a target vessel such as the LAD are also considered part of the target vessel.

Note: In the EVOLVE 48 trial, the ramus will be considered to be a branch of the LCX for purposes of determining eligibility and for determining TVR.

TARGET VESSEL FAILURE

Target vessel failure is any ischemia-driven revascularization of the target vessel, MI (Q-wave and non–Q-wave) related to the target vessel or death related to the target vessel. For the purposes of this protocol, if it cannot be determined with certainty whether the MI or death was related to the target vessel, it will be considered a TVF.

TARGET VESSEL REVASCULARIZATION

Target vessel revascularization is defined as a TLR (see definition above) or a TVR remote (see definition below).

TARGET VESSEL REVASCULARIZATION REMOTE

Target vessel revascularization remote is any ischemia-driven repeat percutaneous intervention, to improve blood flow, or bypass surgery of not previously existing lesions diameter stenosis ≥50% by QCA in the target vessel, excluding the target lesion. A TVR will

be considered ischemia-driven if the target vessel diameter stenosis is ≥50% by QCA and any of the following are present:

- The subject has a positive functional study corresponding to the area served by the target vessel.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target vessel.

A TVR will also be considered as ischemia-driven if the lesion diameter stenosis is ≥70% even in the absence of clinical or functional ischemia.

TECHNICAL SUCCESS

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

TECHNICIAN WORKSHEET

A Technician Worksheet is a record for listing the filming sequence and angulations of x-ray equipment, details of inflations, and description of lesion(s).

THROMBUS (ANGIOGRAPHIC)

Thrombus (angiographic) is discrete, mobile intraluminal filling with defined borders with/without associated contrast straining, classified as either absent or present.

THROMBOLYSIS IN MYOCARDIAL INFARCTION CLASSIFICATION

- TIMI 0: No perfusion.
- TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis of the duration of the cine run.
- TIMI 2: Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
- TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

TOTAL OCCLUSION

A total occlusion is a lesion with no flow (i.e., TIMI flow 0).

TRANSIENT ISCHEMIC ATTACK

A TIA is a focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.

UNANTICIPATED ADVERSE DEVICE EFFECT (*Ref: 21CFR Part 812*)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including

a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (*Ref: ISO 14155 and MEDDEV 2.7/3*)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.