EVOLVE Short DAPT Study (S2073)

A prospective, multicenter, single-arm study designed to assess the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System)

CLINICAL PROTOCOL

IDE # G150194

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Investigational Sites	A list of investigational sites is maintained and will be made available to investigational sites
Vendors	A list of vendors involved in the trial is maintained and will be made available to investigational sites

Original Release: August 27, 2015
Current Version: April 12, 2017

2. Protocol Synopsis

EVOLVE Short DAPT Study (S2073)

EVOLVE Short DAPT Study: A prospective, multicenter, single-arm study designed to assess the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System)	
Primary Objective	To assess the safety of 3-month DAPT in subjects at high risk for bleeding undergoing PCI with the SYNERGY Stent System
Study Design	Prospective, Multicenter, Single-Arm, Historical Control, Propensity Score Approach
Planned Number of Subjects	Up to 2,250 subjects will be enrolled in the EVOLVE Short DAPT Study
Planned Number of Sites / Countries	Up to 120 sites worldwide in the United States, Europe, Japan, and Brazil
Test Device	SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System)
Device Sizes	The SYNERGY commercial device matrix consists of the following sizes: Available Stent Lengths (mm): 8, 12, 16, 20, 24, 28, 32, 38 Available Stent Diameters (mm): 2.25, 2.50, 2.75, 3.00, 3.50, 4.00

Co-Primary Endpoints	The study has two co-primary endpoints that will be assessed. They are: • Rate of death or myocardial infarction (MI) between 3 and 15 months • Rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) involving SYNERGY between 3 and 15 months
Secondary Endpoint	• Rate of bleeding, based upon the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) between 3 and 15 months in subjects not taking chronic anticoagulation.
Additional Endpoints	The following clinical endpoints will be measured at 3 months, 6 months, 12 months and 15 months: • Rate of major adverse cardiac & cerebrovascular events (MACCE), defined as the composite of all death, MI, and stroke • Rate of major adverse cardiac events (MACE), defined as the composite of cardiac death, MI and TVR • Rate of target vessel failure (TVF), defined as the composite of TVR, cardiac death or target vessel related MI • Rate of cardiac death/MI • Rate of bleeding (GUSTO definition) • Rate of bleeding (BARC definition) • Rate of bleeding (TIMI definition) • Rate of stent thrombosis (ARC definite/probable) • Rate of cardiac death • Rate of non-cardiac death • Rate of all cause death • Rate of death/MI • Rate of MI (Q-wave and non–Q-wave) • Rate of stroke, ischemic and hemorrhagic • Rate of Target Vessel Revascularization (TVR) • Rate of Target Lesion Revascularization (TLR) • Rate of MI (ST-related and not ST-related)

Follow-up Schedule	Follow-up will be performed (either by telephone or office visit) at the following milestones: • 3 months (90 days following the index or staged procedure, if applicable + 30 days or - 7 days) • 6 months (90 days following the 3-month visit date* ± 30 days) • 12 months (270 days following the 3-month visit date* ± 30 days) • 15 months (365 days following the 3-month visit date* + 30 days) All enrolled subjects are to be followed at all milestones through 15 months. The study will be considered complete with regard to the primary endpoints after all subjects have completed the 15-month follow-up. *If a 3-month visit is missed for a subject, the future follow-up windows at 6, 12, and 15 months will be calculated based at 180, 360, and 455 days respectively following the index or staged procedure, if applicable.
Study Duration	Enrolled subjects who receive a SYNERGY stent will be followed for 15 months following the index procedure.
Required Medication Therapy	• Aspirin: Subjects should be treated with aspirin for the duration of the trial. The minimum daily maintenance dose of aspirin should be 75–100 mg. • P2Y12 inhibitor: Subjects must be treated with one of the following P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure. • Enrolled subjects must take both aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure. • Enrolled subjects will be evaluated at 3 months to confirm that discontinuation of P2Y12 inhibitor remains appropriate. • Subjects who are eligible for discontinuation of P2Y12 inhibitor therapy at 3 months are required to take aspirin starting at 3 months and continuing for the duration of the study.

Enrollment Inclusion Criteria	1. Subject is considered at high risk for bleeding, defined as meeting one or more of the following criteria at the time of enrollment: • ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit, • history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure, • history of stroke (ischemic or hemorrhagic), • renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent), • platelet count ≤100,000/μL 2. Subject must be at least 18 years of age 3. Subject must have had implantation of at least one SYNERGY stent within the preceding 3 calendar days 4. Subject must be able to take study required antiplatelet therapy (as required per protocol) 5. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at the 3-month milestone, if eligible per protocol 6. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any study-specific procedures are performed 7. For subjects less than 20 years of age enrolled at a Japanese site, the subject/ the subject's legal representative must provide written informed consent before any study-specific tests or procedures are performed
Enrollment Exclusion Criteria	1. Subject who is taking (or is planning to take) chronic or lifelong anticoagulation within 15 months following index procedure. 2. Subject with an indication for the index procedure of acute ST elevation MI (STEMI) 3. Subject with an indication for the index procedure of Non ST elevation MI (NSTEMI), based on the 3rd Universal MI definition (1) 4. Subject with treatment with another coronary stent, other than SYNERGY, during the index procedure 5. Subject with planned staged procedures. (Note: Planned staged procedures are allowed if performed within 7 days and with only SYNERGY stents). 6. Subject has a known allergy to contrast (that cannot be adequately pre-

	medicated), the SYNERGY stent system or protocol-required concomitant medications (e.g., everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors and aspirin) 7. Subject with implantation of a drug-eluting stent within 9 months prior to index procedure 8. Subject previously treated at any time with intravascular brachytherapy 9. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding 10. Subject is participating in an investigational drug or device clinical trial that has not reached its primary endpoint (Note: registry, observational, data collection studies are not exclusionary) 11. Subject intends to participate in an investigational drug or device clinical trial within 15 months following the index procedure (Note: registry, observational, data collection studies are not exclusionary) 12. Subject judged inappropriate for discontinuation from P2Y12 inhibitor use at 3 months, due to another condition requiring chronic P2Y12 inhibitor use 13. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 3 months following index procedure 14. Subject is a woman who is pregnant or nursing 15. Subject with a current medical condition with a life expectancy of less than 15 months 16. Target lesion(s) is located in the left main 17. Target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate 18. Subject has unprotected left main coronary artery disease (> 50% diameter stenosis) 19. Planned treatment of more than 3 lesions 20. Planned treatment of lesions in more than 2 major epicardial vessels 21. Target lesion(s) treated that involves a complex bifurcation (i.e. bifurcation lesion requiring treatment with more than one stent) 22. Target lesion(s) is restenotic from a previous stent implantation 23. Target lesion(s) is located within a saphenous vein graft or an arterial graft 24. Target lesion(s) with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing 25. Thrombus, or possible thrombus, present in the target vessel (by visual

	estimate)
Staged Procedure(s)	• Planned staged procedures are allowed if performed ≤ 7 days from the index procedure and with only SYNERGY stents. • Subjects with a planned staged procedure > 7 days from the index procedure or with stents other than SYNERGY must not be enrolled in the study. • A staged procedure is only permitted when all enrollment inclusion criteria and no enrollment exclusion criteria are met for all lesions treated during both the initial procedure and the subsequent staged procedure. • The total number of lesions treated during the index and staged procedures combined must not exceed 3. • The total number of epicardial vessels treated during the index and staged procedures combined must not exceed 2. • In the case of a staged procedure meeting these criteria, the subject should return for the 3-month visit (i.e. assessment for eligibility to discontinue P2Y12 inhibitor) 90 days following the staged procedure + 30 days or - 7 days.
Eligible for Discontinuation of P2Y12 Inhibitor at 3 Months	Subjects are eligible for discontinuation of P2Y12 inhibitor at 3 months if they meet <u>both</u> of the following criteria: • Subject was treated with 3 months of P2Y12 inhibitor/aspirin post index procedure. (Note: Subjects enrolled under a prior version of the protocol who were on chronic anticoagulation between 0-3 months are eligible if they were also taking P2Y12 inhibitor or P2Y12 inhibitor/aspirin between 0-3 months). • Subject was free from events (stroke, MI, PCI, CABG, and stent thrombosis) between the index procedure and the 3 month visit

Not Eligible for Discontinuation of P2Y12 Inhibitor at 3 Months	Subjects are not eligible for discontinuation of P2Y12 inhibitor at 3 months if any of the following criteria are met: • Subject who experiences a stroke, MI, PCI, CABG and/or stent thrombosis, during the 0-3 month period (between the date of the index procedure and the date of the 3-month follow-up visit) • Subject who is non-compliant with P2Y12 inhibitor or aspirin during the 0-3 month period (between the date of the index procedure and the date of the 3-month follow-up visit). (Note: Subjects enrolled under a prior version of the protocol who were on chronic anticoagulation between 0-3 months are not eligible if they were not taking P2Y12 inhibitor or P2Y12 inhibitor/aspirin between 0-3 months). Non-compliant defined as: o Taking less than 80% or greater than 120% (subject reported); and/or o Interruption for 14 or more consecutive days • Subject judged inappropriate for discontinuation from P2Y12 inhibitor use at 3 months due to another condition requiring chronic P2Y12 inhibitor use Note: All enrolled subjects who receive a SYNERGY stent must be followed at all milestones through 15-months, regardless of eligibility to discontinue P2Y12 inhibitor. Note: Compliance to the use of P2Y12 inhibitor and aspirin will be ascertained from the subject interview at the 3-month follow-up visit and will be used to determine if the subject is eligible for discontinuation of P2Y12 inhibitor. During the interview, the subject will also be asked about any significant interruptions (3 days or greater) in the prescribed treatment since the last follow-up visit.
Management of Endpoint Events after 3 months	Following the 3-month milestone, subjects who experience MI or stent thrombosis events should be treated per the investigator's discretion and should be followed through the 15-month visit.
Safety Parameters	• All serious adverse events (SAE), adverse device effects (ADE), death, MI, TVR, stroke, stent thrombosis, and bleeding events 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

Statistical Methods	
Co-Primary Endpoint (Death/MI) Statistical Hypothesis	The 3 to 15 month death/MI rate for SYNERGY with 3-month DAPT (test group) is non-inferior compared to historical drug-eluting stents (DES) with 12-month DAPT (control group) in subjects at high risk for bleeding.
Co-Primary Endpoint (Death/MI) Statistical Test Method	A Propensity Score (PS) Model using quintile adjustment will be used to test the hypothesis of non-inferiority of SYNERGY with 3-month DAPT (test group) compared to historical DES with 12-month DAPT (control group) H_0: $P_{Death/MI-3M} - P_{Death/MI-12M} \geq \Delta$ H_1: $P_{Death/MI-3M} - P_{Death/MI-12M} < \Delta$ where $P_{Death/MI-3M}$ and $P_{Death/MI-12M}$ are the 3 to 15-month death/MI rates for the 3-month DAPT test group and 12-month DAPT group (historical control), respectively, and Δ is the non-inferiority margin.
Co-Primary Endpoint (Death/MI) Sample Size Parameters	• Expected 3 to 15 month death/MI rate in subjects at high risk for bleeding with 12-month DAPT (control) = 5.6%[a] • Expected 3 to 15 month death /MI rate in subjects at high risk for bleeding with 3-month DAPT (test) = 5.6%[a] • Non-inferiority margin = 2.52% (45% relative to the expected rate) • Test significance level = 0.025 (1-sided) • Power = 85% • The unadjusted comparison requires a minimum of 1,500 evaluable subjects per group, which is based on equal allocation using 2-group test of equivalence in proportions in nQuery Advisor • Control subjects are historical -limus DES subjects who were at high risk for bleeding extracted from Boston Scientific (BSC) sponsored trials PROMUS Element Plus US Post Approval Study (PE+PAS), PE PROVE European Post Approval Study, and the HCRI DAPT Study minus TAXUS subjects. The number of available historical control subjects is approximately 1,643 (403 from BSC + 1,240 from HCRI DAPT) • Number of evaluable test subjects required in the propensity score model is 1,650 (1,500 *1.1) including additional 10% subjects accounting for model variability • Expected drop out rate due to ineligibility for 3 month DAPT in 0 to 3 months = 15% • Expected attrition rate in 3 to 15 months = 3%

	• N = 2,000[b] subjects enrolled [a]The expected rate of 5.6% for 3 to 15-month death/MI is estimated from BSC PROMUS subjects at high risk for bleeding extracted from the HCRI DAPT Study (13/253), PE+ US Post Approval Study (14/318), and PE PROVE European Post Approval Study (11/85). [b]The enrollment may be terminated early if the observed dropout rate in 0 to 3 months is projected to be <15%. Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate in 0 to 3 months is projected to be >15%.
Co-Primary Endpoint (Stent Thrombosis) Statistical Hypothesis	Rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) involving SYNERGY between 3 and 15 months in subjects at high risk for bleeding is less than the performance goal (PG) of 1%
Co-Primary Endpoint (Stent Thrombosis) Statistical Test Method	An exact test will be used to test the hypothesis of one sample proportion compared to a PG: H_0: $P_{ST\text{-}3M} \geq PG$ H_1: $P_{ST\text{-}3M} < PG$ where $P_{ST\text{-}3M}$ is the 3 to 15-month ARC-defined (definite/probable) ST (involving SYNERGY) rate for the 3-month DAPT group and PG is the performance goal.
Co-Primary Endpoint (Stent Thrombosis) Sample Size Parameters	• Expected 3 to 15-month rate of ST (involving SYNERGY) in subjects at high risk for bleeding from 3-month DAPT (test) < 0.4% • PG = 1% • Test significance level = 0.025 (1-sided) • Power = 80% • Number of evaluable subjects = 1,650 • Expected drop out rate due to ineligibility for 3 month DAPT in 0 to 3 months = 15%[a] • Expected attrition rate in 3 to 15 months = 3% • N = 2,000[b] enrolled subjects required [a]The enrollment may be terminated early if the observed dropout rate in 0 to 3 months is projected to be <15%. Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate in 0 to 3 months is projected to be >15%.
Secondary Endpoint (Bleeding) Statistical Hypothesis	The 3 to 15 month rate of bleeding, based upon the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) for SYNERGY in subjects at high risk for bleeding (excluding subjects on chronic anticoagulants)- following 3 month DAPT (test group) is superior compared to historical DES with 12-month DAPT (control group)

Secondary Endpoint (Bleeding) Statistical Test Method	A Propensity Score (PS) Model using quintile adjustment will be used to test the one-sided hypothesis of superiority of SYNERGY with 3-month DAPT (test group) compared to historical DES with 12-month DAPT (control group) H_0: $P_{MB\text{-}3M} - P_{MB\text{-}12M} \geq 0$ H_1: $P_{MB\text{-}3M} - P_{MB\text{-}12M} < 0$ where $P_{MB\text{-}3M}$ and $P_{MB\text{-}12M}$ are the 3 to 15-month bleeding rates for the 3-month DAPT test group and the 12-month DAPT control group, respectively.
Secondary Endpoint (Bleeding) Sample Size Parameters	• Expected 3 to 15 month bleeding rate from 12-month DAPT (control) = 4%[a] • Expected 3 to 15 month bleeding rate from 3-month DAPT (test) = 2.19% • Test significance level = 0.025 (1-sided) • Control subjects are historical -limus DES treated subjects at high risk for bleeding obtained from the HCRI DAPT study, number of available historical control subjects is approximately 1,240 • Number of evaluable test subjects in the propensity score model is 1,650 (including additional 10% subjects accounting for model variability) • Power = 80% using chi-square test (unadjusted power for 1,240 vs 1,650) • Expected drop out rate due to ineligibility for 3 month DAPT in 0 to 3 months = 15% • Expected attrition rate in 3 to 15 months = 3% • N = 2,000[b] subjects enrollment [a]The expected rate for 3 to 15-month bleeding rate is estimated from the BSC PROMUS subjects at high risk for bleeding enrolled in the HCRI DAPT study (10/253). [b]The enrollment may be terminated early if the observed dropout rate in 0 to 3 months is projected to be <15%.
Study Success Criteria	The study will be considered a success if both the co-primary endpoints of death/MI and ARC definite/probable stent thrombosis are met.

3. Table of Contents

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4. Introduction

The EVOLVE Short DAPT Study is designed to assess the safety of 3-month dual antiplatelet therapy (DAPT) in subjects who are at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent System. 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.

Drug-eluting stents delivering anti-proliferative drugs from a durable polymer have significantly reduced angiographic and clinical measures of restenosis compared with bare metal stents (BMS), with no apparent increase in the risk of adverse events (AEs) including death and myocardial infarction (MI) (2-20). However, durable polymers have been associated with hypersensitivity reactions, delayed healing and incomplete endothelialization which, compared to BMS, may contribute to an increased risk of late (30 days to 1 year) and very late (beyond 1 year) stent thrombosis (ST), especially with first generation DES (21-23). Although newer durable polymers may have enhanced biocompatibility and appear to be associated with improved clinical outcomes, they have still been incriminated in the occurrence of inflammation, neoatherosclerosis, and thrombosis (24,25).

To reduce the risk of stent thrombosis, clinical guidance documents recommend DAPT following DES implantation. The American College of Cardiology/American Heart Association recommends that, following DES implantation, patients with stable ischemic heart disease should receive clopidogrel (or an alternative P2Y12 inhibitor) in addition to aspirin for a minimum of 6 months, unless there is a high bleeding risk. Following DES implantation, patients with stable ischemic heart disease who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable (26) Due to the potential for increased risk of ST with durable polymer DES, the recommended duration of DAPT is typically longer with DES compared to BMS (26,27). The recent DAPT study suggested that even longer duration DAPT therapy (≥30 months) provide additional ischemic event reduction (28). However, this study only included durable polymer DES and BMS and patients with high risk of bleeding were mainly excluded. A number of meta-analyses have been performed examining the impact of prolonged DAPT after DES implantation on clinical outcomes (pooling data from 10 trials with >30,000 participants)(29-33). The meta-analyses concluded that a longer duration of DAPT was associated with a lower risk of definite/probable ST and MI compared with a shorter duration of DAPT, however, the benefit of longer-term DAPT on ST was significantly attenuated with use of second-generation DES compared with first generation DES (31). Longer DAPT duration was associated with a significantly higher risk of bleeding and all-cause mortality compared with shorter DAPT (29-33). The optimal duration of DAPT in patients at high risk of bleeding remains unknown.

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, with low initial polymer load, 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 (34,35).

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 (36-51). The EVOLVE series of trials including EVOLVE, EVOLVE II, and EVOLVE II QCA, have established the safety and effectiveness of the SYNERGY Stent System demonstrating that SYNERGY is comparable in performance to the commercially available PROMUS Element stent 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 sent (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)(34). 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 (52,53). The study is now considered complete with regard to the primary endpoint and follow-up through 4 years is complete (54). There were no significant differences between PROMUS Element and either SYNERGY stent for any major cardiac endpoint through 4 years (52,54,55)_ENREF_35_ENREF_35. Additional follow-up is ongoing to 5 years.

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 (56).

- 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 (57).

- 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) (58).

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 Short DAPT Study is designed to assess the safety of a 3 month DAPT regimen following implantation of the SYNERGY stent in a population of patients at high risk for bleeding where a longer DAPT duration might not be appropriate.

5. Device Description

5.1. *SYNERGY Stent System Description*

The SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System) 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).

5.1.1. Device Component Description

The SYNERGY Stent System consists of a platinum chromium stent platform with an abluminal drug/polymer coating mounted onto a Monorail or Over-the-Wire Delivery System. There are three stent models available for the SYNERGY stent:

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

5.1.2. Drug/Polymer Component Description

5.1.2.1. Everolimus

Everolimus is the active pharmaceutical ingredient in the SYNERGY stent. Everolimus possesses anti-fungal, immunosuppressive and anti-proliferative properties. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. Everolimus binds to cytosolic FKBP12 and subsequently inhibits activation of the regulatory kinase mTOR (mammalian target of rapamycin). This inhibition results in cell arrest at the late G1 phase in the cell cycle and thereby impedes functions that govern cell metabolism, growth, and proliferation. Everolimus has been evaluated in clinical trials in the United States (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.

5.1.2.2. 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 Matrix*

The SYNERGY stent system is approved and commercially available. In the EVOLVE Short DAPT Study, clinical sites will select devices from the commercial inventory. The SYNERGY device matrix consists of the following sizes (stent diameter and stent length):

		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

5.3. *Device Labeling*

A basic description of the SYNERGY device and a comprehensive set of Directions for Use (DFU) are contained in each product package or are available electronically, per local regulation, on a Boston Scientific website.

6. Primary Objective

The primary objective of the EVOLVE Short DAPT Study is to assess the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk for bleeding undergoing percutaneous coronary intervention (PCI) with the SYNERGY Stent System.

7. Endpoints

7.1. *Co-Primary Endpoints*

- Rate of death or myocardial infarction (MI) between 3 and 15 months
- Rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) (8) involving SYNERGY between 3 and 15 months

7.2. *Secondary Endpoint*

- Rate of bleeding, based upon the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) (59),between 3 and 15 months in subjects not taking chronic anticoagulation.

7.3. *Additional Endpoints*

The following clinical endpoints will be measured at 3 months, 6 months, 12 months and 15 months:

- Rate of major adverse cardiac & cerebrovascular events (MACCE), defined as the composite of all death, MI, and stroke
- Rate of major adverse cardiac events (MACE), defined as the composite of cardiac death, MI and TVR
- Rate of target vessel failure (TVF), defined as the composite of TVR, cardiac death or target vessel related MI
- Rate of cardiac death/MI
- Rate of bleeding (GUSTO definition) (60)
- Rate of bleeding (BARC definition) (59)
- Rate of bleeding (TIMI definition) (61)
- Rate of stent thrombosis (ARC definite/probable)
- Rate of cardiac death
- Rate of non-cardiac death
- Rate of all cause death
- Rate of death/MI

- Rate of MI (Q-wave and non–Q-wave)
- Rate of stroke, ischemic and hemorrhagic
- Rate of Target Vessel Revascularization (TVR)
- Rate of Target Lesion Revascularization (TLR)
- Rate of MI (ST-related and not ST-related)

8. Design

The EVOLVE Short DAPT Study is a prospective, multicenter, single-arm study, using a historical control and a propensity score approach to assess the safety of 3-month DAPT in subjects at high risk for bleeding undergoing PCI with a SYNERGY Stent System

8.1. *Scale and Duration*

The EVOLVE Short DAPT Study will be conducted at up to 120 sites worldwide in the United States, Europe, Japan, and Brazil with planned enrollment of up to 2,250 subjects. Follow-up will be required at the following time points: 3 months, 6 months, 12 months and 15 months.

A schematic of the EVOLVE Short DAPT Study is shown on the following page in Figure 8.1-1.

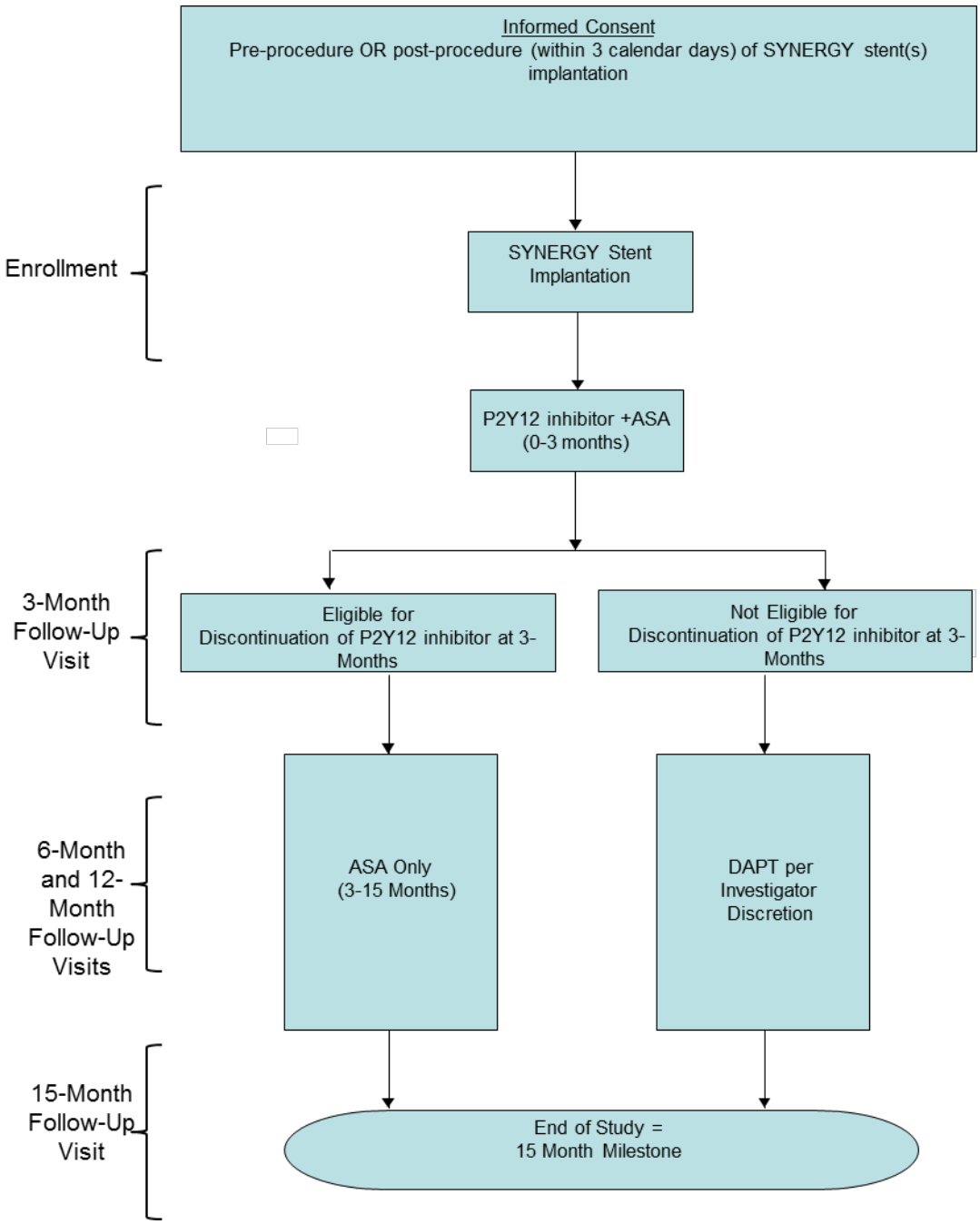

Figure 8.1-1: EVOLVE Short DAPT Study

8.2. *Treatment Assignment*

A subject is considered enrolled once the Institutional Review Board (IRB)/Ethics Committee (EC) approved study informed consent form (ICF) has been signed and the subject has received at least one commercial SYNERGY stent. Enrolled subjects must meet all inclusion and no exclusion criteria. Enrollment should occur within 3 calendar days of the index procedure date.

8.2.1. Treatment

Subjects should be treated per physician discretion and standard of care with the exception of the protocol requirement for DAPT. The sites' commercial device supply will be used.

8.3. *Justification for the Study Design*

Based on the novel design feature of the SYNERGY stent (polymer resorption occurring soon after completion of drug release at 90 days), it is expected that planned treatment with 3 months of DAPT in in the defined population of patients at high risk of bleeding will be safe, and may result in benefits such as avoidance of bleeding, cost and delay of non-cardiac procedures relative to a strategy of longer-term DAPT in the setting of current durable polymer drug-eluting stents.

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 Short DAPT Study. The design includes a large historical control cohort, instead of a traditional randomized trial, resulting in a smaller overall sample size, without sacrificing sensitivity to detect adverse events in the experimental arm.

9. Subject Selection

9.1. *Study Population and Eligibility*

Inclusion and exclusion criteria for the EVOLVE Short DAPT Study are included in Table 9.2-1 and Table 9.3-1 respectively. Prior to enrollment in the trial, a subject must meet all of the inclusion criteria and none of the 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 criteria (see Section 9.3) are met

Table 9.2-1: Inclusion Criteria

Inclusion Criteria	1. Subject is considered at high risk for bleeding, defined as meeting one or more of the following criteria at the time of enrollment: • ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit, • history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure, • history of stroke (ischemic or hemorrhagic), • renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent), • platelet count ≤100,000/μL 2. Subject must be at least 18 years of age 3. Subject must have had implantation of at least one SYNERGY stent within the preceding 3 calendar days 4. Subject must be able to take study required antiplatelet therapy (as required per protocol) 5. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at the 3-month milestone, if eligible per protocol 6. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any study-specific procedures are performed 7. For subjects less than 20 years of age enrolled at a Japanese site, the subject/ the subject's legal representative must provide written informed consent before any study-specific tests or procedures are performed

9.3. *Exclusion Criteria*

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

	1. Subject who is taking (or is planning to take) chronic or lifelong anticoagulation within 15 months following index procedure. 2. Subject with an indication for the index procedure of acute ST elevation MI (STEMI) 3. Subject with an indication for the index procedure of Non ST elevation MI (NSTEMI), based on the 3rd Universal MI definition (1) 4. Subject with treatment with another coronary stent, other than SYNERGY, during the index procedure 5. Subject with planned staged procedures. (Note: Planned staged procedures are allowed if performed within 7 days and with only SYNERGY stents). 6. Subject has a known allergy to contrast (that cannot be adequately pre-medicated), the SYNERGY stent system or protocol-required concomitant medications (e.g., everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors and aspirin) 7. Subject with implantation of a drug-eluting stent within 9 months prior to index procedure 8. Subject previously treated at any time with intravascular brachytherapy 9. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding 10. Subject is participating in an investigational drug or device clinical trial that has not reached its primary endpoint (Note: registry, observational, data collection studies are not exclusionary) 11. Subject intends to participate in an investigational drug or device clinical trial within 15 months following the index procedure (Note: registry, observational, data collection studies are not exclusionary)

Table 9.3-1: Exclusion Criteria

Exclusion Criteria	12. Subject judged inappropriate for discontinuation from P2Y12 inhibitor use at 3 months, due to another condition requiring chronic P2Y12 inhibitor use 13. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 3 months following index procedure 14. Subject is a woman who is pregnant or nursing 15. Subject with a current medical condition with a life expectancy of less than 15 months 16. Target lesion(s) is located in the left main 17. Target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate 18. Subject has unprotected left main coronary artery disease (> 50% diameter stenosis) 19. Planned treatment of more than 3 lesions 20. Planned treatment of lesions in more than 2 major epicardial vessels 21. Target lesion(s) treated that involves complex bifurcation (i.e. bifurcation lesion treated with more than one stent) 22. Target lesion(s) is restenotic from a previous stent implantation 23. Target lesion(s) is located within a saphenous vein graft or an arterial graft 24. Target lesion(s) with a TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing 25. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)

10. Subject Accountability

10.1. Point of Enrollment

A subject is considered enrolled once the Institutional Review Board (IRB)/Ethics Committee (EC) approved study informed consent form (ICF) has been signed and the subject has received at least one commercial SYNERGY stent. Enrolled subjects must meet all inclusion and no exclusion criteria. Enrollment should occur within 3 calendar days of the index procedure date.

10.2. *Withdrawal*

All subjects enrolled in the clinical trial (including those withdrawn from the clinical trial or lost to follow-up) shall be accounted for and documented. 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. All applicable case report forms (CRFs) up to the point of subject withdrawal, including the End of Study CRF must be completed. Subjects who are "lost to follow-up" should have documented attempts to contact them prior to the completion of the End of Study CRF. Additional data will no longer be collected after the point at which a subject withdraws his/her consent. Data collected up to the point of subject withdrawal may be used.

11. Study Methods

11.1. *Data Collection*

The data collection schedule for the EVOLVE Short DAPT Study is summarized below:

	Pre-Index Procedure	Index Proc-edure	Post-Procedure /Pre Discharge	Follow-Up Visits			
				3-month Office or Telephone	6-month Office or Telephone	12-month Office or Telephone	15-month Office or Telephone
Informed Consent[1]		X					
Demography		X					
Medical History		X					
Cardiac Biomarkers (CK, CK-MB, and/or troponin)	X[2]		X[3]				
Angiography/ Stent Implantation		X					
Assessment of Eligibility to Discontinue P2Y12 Inhibitor				X			
DAPT Medication Data Collection	X	X	X	X	X	X	X
ADE, SAE, SADE, UADE, USADE, and device deficiency assessment		X	X	X	X	X	X
Endpoint Event (MACCE, ST, bleeding) Assessment		X	X	X	X	X	X

[1] Consent can be obtained either pre-procedure or post-procedure (up to 3 calendar days after the index procedure). If the study Informed Consent Form is modified during the course of the trial, study subjects will be re-consented, if necessary.

[2] If performed per standard of care, pre-procedure cardiac enzymes (CK, CK-MB, and/or troponin within 72 hours prior to the index procedure) should be recorded in the EDC system. If more than one draw was performed within 72 hours, only the most recent value should be recorded in EDC.

[3] If performed per standard of care, post-procedure cardiac enzymes (CK, CK-MB, and/or troponin between 12-24 hours following index procedure or prior to discharge, if discharged prior to the 12 hours) should be recorded in the EDC system. Only peak values should be recorded in EDC.

11.2. *Study Candidate Screening*

Study investigators are expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

A screening log will be maintained to document selected information about consented subjects who fail to meet the EVOLVE Short DAPT Study criteria, including the reason for screen failure.

11.3. *Informed Consent*

Subjects who meet the enrollment eligibility criteria will be asked to sign the IRB/EC-approved study informed consent form (ICF). Subjects must be given ample time to review the ICF and have questions answered before signing. Informed consent must be obtained prior to the subject's index procedure or within 3 calendar days following the index procedure, prior to any subject data entry into EDC. The date of index procedure is considered day 0 and enrollment can occur as late as day 3.

Refer to section 10.1 for definition of point of enrollment.

11.4. *Antiplatelet Medications*

Antiplatelet medications (aspirin + P2Y12 inhibitor) must be reported in the electronic case report form (eCRF) from 72 hours prior to the index procedure through the end of the study. Information pertaining to the use of antiplatelet medications including dose changes, medication interruptions (3 days or greater), and medication cessation, must be documented.

11.4.1. 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.

11.4.2. 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. *Laboratory Procedures*

If performed per standard of care, results of the following laboratory tests will be recorded in the study electronic data capture system (EDC):

- Before the index procedure (within 72 hours prior to the index procedure), a CK, CK-MB, and/or troponin. If more than one draw was performed within 72 hours, only the most recent value should be recorded in EDC.
- A post-procedural (12 - 24 hours post-index procedure or prior to discharge, if hospitalized < 12 hours) CK, CK-MB, and/or troponin. Only peak enzyme values should be recorded in EDC.

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.

11.6.1.1. Stent Placement

Stent placement should be performed per local standard practice. Refer to the DFU for detailed instructions about preparation and placement of the SYNERGY stent.

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 baseline, procedural, target lesion and SYNERGY stent information on the appropriate eCRFs.
- Record antiplatelet medications
- Complete AE assessment and collect source documents as described in Section 20.

11.8. *Postprocedure/Prehospital Discharge*

- 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.

- P2Y12 inhibitor: Subjects should be treated with one of the following P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure.

- Enrolled subjects must take both aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure.

- Enrolled subjects will be evaluated at 3 months to confirm that discontinuation of P2Y12 inhibitor remains appropriate.
- Subjects who are eligible for discontinuation of P2Y12 inhibitor therapy at 3 months are required to take aspirin starting at 3 months and continuing for the duration of the study.
- The subject may be discharged from the hospital when clinically stable at the Investigator's discretion. Generally, this is ≤ 24 hours post index procedure but standard, local practice should be followed.
- 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/respond for follow-up assessments according to the trial event schedule. Study staff should establish a date for the follow-up visit with the subject and if possible, schedule the visit(s) at the time of hospital discharge.

11.9. *Staged Procedures*

- Planned staged procedures are allowed if performed ≤ 7 days from the index procedure and with only SYNERGY stents.
- Subjects with a planned staged procedure > 7 days from the index procedure or with stents other than SYNERGY must not be enrolled in the study.
- A staged procedure is only permitted when all enrollment inclusion criteria and no enrollment exclusion criteria are met for all lesions treated during both the initial procedure and the subsequent staged procedure.
- The total number of lesions treated during the index and staged procedures combined must not exceed 3.
- The total number of major epicardial vessels treated during the index and staged procedures combined must not exceed 2.
- In the case of a staged procedure meeting these criteria, the subject should return for the 3-month visit (i.e. assessment for eligibility to discontinue P2Y12 inhibitor) 90 days following the staged procedure + 30 days or - 7 days.

11.10. *Follow-Up*

All enrolled subjects who receive a SYNERGY stent will be evaluated in-hospital and at 3 months, 6 months, 12 months and 15 months after the index procedure.

All protocol-required follow-up assessments must be conducted with direct contact with the subjects by a trained study team member, documented on the Delegation of Authority log. In order to allow for flexibility to encourage subject retention, follow-up assessments may be performed via telephone interview or office visit as per local practice. 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.

11.10.1. 3-Month Follow-up (90 days following the index or staged procedure, if applicable + 30 days or – 7 days)

All enrolled subjects must be evaluated 3 months after the index or staged (if applicable) procedure. The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 3-month follow-up, the following assessments must be completed.

- AE assessment and source document collection as described in Section 20.
- Documentation of current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions (3 days or greater), and medication cessation must be documented.
- Assessment of subject's eligibility to discontinue P2Y12 inhibitor. Investigator involvement in the assessment to discontinue P2Y12 inhibitor is required.
- If a subject meets criteria, the subject should discontinue P2Y12 inhibitor at the time of the 3-month follow-up visit and should continue taking aspirin through the end of the study.

  All enrolled subjects should be followed at all milestones through 15-months, regardless of eligibility to discontinue P2Y12 inhibitor

11.10.1.1. Eligible for Discontinuation of P2Y12 Inhibitor at 3 Months

Subjects are eligible for discontinuation of P2Y12 inhibitor at 3 months if they meet both of the following criteria:

- Subject was treated with 3 months of P2Y12 inhibitor/aspirin post index procedure. (Subjects enrolled under a prior version of the protocol who were on chronic anticoagulation between 0-3 months are eligible if they were also taking P2Y12 inhibitor or P2Y12 inhibitor/aspirin between 0-3 months).
- Subject was free from events (stroke, MI, PCI, CABG, and stent thrombosis) between the index procedure and the 3-month visit

11.10.1.2. Not Eligible for Discontinuation of P2Y12 Inhibitor at 3 Months

Subjects are not eligible for discontinuation of P2Y12 inhibitor at 3 months if any of the following criteria are met:

- Subject who experiences a stroke, MI, PCI, CABG and/or stent thrombosis, during the 0-3 month period (between the date of index procedure and the date of the 3-month follow-up visit)
- Subject who is non-compliant with P2Y12 inhibitor or aspirin during the 0-3 month period (between the date of the index procedure and the date of the 3-month follow-up visit). Subjects enrolled under a prior version of the protocol who were on chronic anticoagulation between 0-3 months are not eligible if they were not taking P2Y12 inhibitor or P2Y12 inhibitor/aspirin between 0-3 months.

  Non-compliant defined as:

  - Taking less than 80% or greater than 120% (subject reported); and/or

- Interruption for 14 or more consecutive days

- Subject judged inappropriate for discontinuation from P2Y12 inhibitor use at 3 months due to another condition requiring chronic P2Y12 inhibitor use

Compliance to the use of P2Y12 inhibitor and aspirin will be ascertained from the subject interview at the 3-month follow-up visit and will be used to determine if the subject is eligible for discontinuation of P2Y12 inhibitor. During the interview, the subject will also be asked about any significant interruptions (3 days or greater) in the prescribed treatment since the last follow-up visit.

Note: All enrolled subjects who receive a SYNERGY stent must be followed at all milestones through 15-months, regardless of eligibility to discontinue P2Y12 inhibitor.

11.10.2. 6-Month Follow-up (90 days following the 3-month visit date ± 30 days)

All enrolled subjects must be evaluated approximately 6 months after the index procedure (3 months after the 3-month visit). 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.

- AE assessment and source document collection as described in Section 20.
- Documentation of current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions (3 days or greater), and medication cessation must be documented.

11.10.3. 12-Month Follow-up (270 days following the 3-month visit date ± 30 days)

All enrolled subjects must be evaluated approximately 12 months after the index procedure (9 months after the 3-month visit). 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.

- AE assessment and source document collection as described in Section 20.
- Documentation of current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions (3 days or greater), and medication cessation must be documented.

11.10.4. 15-Month Follow-up (365 days following the 3-month visit date* + 30 days)

All enrolled subjects must be evaluated approximately 15 months after the index procedure (12-months after the 3-month visit). The follow-up assessment may be performed via telephone interview with the subject or during an office visit. During the 15-month follow-up, the following assessments must be completed.

- AE assessment and source document collection as described in Section 20.
- Documentation of current antiplatelet medications (P2Y12 inhibitor and aspirin). Information pertaining to dose changes, medication interruptions (3 days or greater), and medication cessation must be documented.

11.10.5. Procedure for Determining When a Subject is Lost to Follow-Up

A subject will not be considered lost to follow-up unless the subject misses the 15-month follow-up visit. A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter) should be made to contact the subject for each missed follow-up visit. This information should be documented in the source.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Co-Primary Endpoints

There are two powered co-primary endpoints:

1. The rate of death or myocardial infarction (MI) between 3 and 15 months expressed as the proportion of subjects who experience death/MI between 3 and 15 months among all subjects who either experience death/MI between 3 and 15 months or survive free of death/MI for at least 425 days.

2. The rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) involving SYNERGY between 3 and 15 months expressed as the proportion of subjects who experience ARC ST between 3 and 15 months among all subjects who either experience ARC ST between 3 and 15 months or survive free of ARC ST for at least 425 days.

12.1.1.1. Hypotheses

Death/MI:

The null hypothesis that the difference of death/MI rates between SYNERGY with 3-month DAPT (test group) and historical DES with 12-month DAPT (control group) is greater than or equal to the non-inferiority margin will be tested against the alternative hypothesis that the difference between test group and control group is less than the non-inferiority margin in subjects at high risk for bleeding:

H_0: $P_{Death/MI\text{-}3M} - P_{Death/MI\text{-}12M} \geq \Delta$

H_1: $P_{Death/MI\text{-}3M} - P_{Death/MI\text{-}12M} < \Delta$

where $P_{Death/MI\text{-}3M}$ and $P_{Death/MI\text{-}12M}$ are the 3 to 15-month death/MI rates for the 3-month DAPT test group and 12-month DAPT group (historical control), respectively, and Δ is the non-inferiority margin.

A propensity score model using quintile adjustment for death/MI will be used to test the hypothesis of non-inferiority of the test group compared to historical control group.

ARC-defined ST:

The null hypothesis that ARC ST rate is greater than or equal to the performance goal will be tested against the alternative hypothesis that ARC ST rate for the is less than the performance goal:

H_0: $P_{ST\text{-}3M} \geq PG$

H_1: $P_{ST\text{-}3M} < PG$

where $P_{ST\text{-}3M}$ is the rate of 3 to 15-month ARC-defined definite/probable ST involving SYNERGY for the 3-month DAPT group, and PG is the performance goal.

12.1.1.2. Sample Size

Death/MI:

The expected rate of 5.6% for 3 to 15 month death/MI rates in subjects at high risk for bleeding for both test and control groups is estimated from BSC PROMUS subjects extracted from the HCRI DAPT, PE+ PAS, and PE PROVE studies. The non-inferiority margin is 2.52%, which is 45% of the expected rate. With one-sided 2.5% significance level, the study will require a minimum of 1,500 evaluable subjects per group to provide 85% power to reject the null hypothesis when the alternative hypothesis is true. With consideration of additional 10% subjects accounting for model variability, number of evaluable subjects in the test group required in the propensity score model is 1,650 (1,500 *1.1). In the control group, there are approximately 1,643 historical -limus DES high risk for bleeding subjects available from Boston Scientific sponsored trials (403) and the HCRI DAPT Study minus TAXUS (1,240). Assuming that the dropout rate due to the ineligibility between 0 and 3 months for 3-month DAPT test group is 15% and the expected attrition rate between 3 and 15 months is 3%, the study needs to enroll 2,000 subjects in the 3-month DAPT test group.

The enrollment may be terminated earlier if the observed dropout rate between 0 and 3 months is projected to be less than 15%. Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate in 0 to 3 months is projected to be >15%.

The sample size calculation is based on 2-group test of equivalence in proportions with equal allocation using nQuery Advisor® Version 5.0

ARC-defined ST:

The expected rate of 3 to 15-month rate of ARC-defined definite/probable ST in subjects at high risk for the test group is less than 0.4% based on HCRI DAPT, PE+ PAS, and PE PROVE studies. The performance goal is set to be 1%. With a one-sided 2.5% significance level, 1,650 evaluable subjects will be required to provide 80% power to reject the null hypothesis when the alternative hypothesis is true. Assuming that the dropout rate due to the ineligibility between 0 and 3 months for the test group is 15% and the expected attrition rate between 3 and 15 months is 3%, the study needs to enroll 2,000 subjects for the test group.

The enrollment may be terminated earlier if the observed dropout rate between 0 and 3 months is projected to be less than 15%. Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate in 0 to 3 months is projected to be >15%.

The sample size is calculated using an exact test for single proportion using nQuery Advisor® Version 5.0.

12.1.1.3. Statistical Methods

Death/MI:
A propensity score model with quintile adjustment will be used to address baseline imbalance between the test group and the historical control group. The null hypothesis will be tested against alternative hypothesis using the propensity score quintile adjusted death/MI co-primary endpoint for testing non-inferiority between the test group and the historical control group.

The propensity score will be estimated by using logistic regression with inclusion of all pre-specified baseline covariates in the model as the predictor variables and the treatment groups (test vs control) as the dependent variable.

The entire study analysis set will be divided into propensity score quintiles. The death/MI co-primary endpoints will be calculated by study group within each quintile. The adjusted measure for each study group is a simple mean of the five propensity score quintile estimates. Similarly, the stratified between-group difference estimate is the mean of the quintile difference estimates, and the adjusted standard error is obtained from the square root of the mean of the five quintile variances.

Let d_i, *i = 1, …, 5* be the quintile difference estimates, se_i, *i = 1, …, 5* are the standard errors of the quintile difference estimates, and var_i, *i = 1, …, 5* are the corresponding variances where $var_i = se_i^2$. The adjusted between-group difference estimate is $\bar{d} = \frac{1}{5}\sum_{i=1}^{5}(d_i)$, $Var(\bar{d}) = \frac{1}{5^2}\sum_{i=1}^{5} var(d_i)$, and $SE(\bar{d}) = \sqrt{Var(\bar{d})}$.

The adjusted between-group difference estimate ($\bar{d}$) and the standard error ($SE(\bar{d})$) of the adjusted between-group difference will be used to construct the 97.5% upper confidence bound of the adjusted between-group difference using normal approximation to binomial (z-test). If the 97.5% upper confidence bound is less than the non-inferiority margin, the null hypothesis will be rejected for the death/MI co-primary endpoint and the test group will be concluded to be non-inferior to historical control group.

The covariates for propensity score model will include the following variables in different categories, which are available in both the short DAPT study and the historical control studies:

Table 12.1-1: Propensity Score Model Covariates

Category	**Covariates**
Geographic Location	region (US vs OUS)
Demographics	age, gender, race/ethnicity
Physical Assessment	height, weight
Medical History	smoking status, medically treated diabetic, hypertension requiring medication, hyperlipidemia requiring medication, history of CHF, history of MI, current angina status (stable/unstable/silent ischemia/none), history of PCI, history of CABG, LVEF, history of CVA, history of renal disease/insufficiency/failure, history of PVD, anticoagulant therapy, history of major bleeding
Target Lesion/ Pre-Procedure*	CASS site, lesion length (visual), RVD (visual), %DS (visual), calcification, tortuosity, per-procedure TIMI flow
Procedure/Post-Procedure	number of vessels treated (index + staged), number of lesions (index + staged), number of stents (index + staged), P2Y12 inhibitor type (0-3 months)
Additional angiographic data*	post-procedure TIMI flow, post-procedure %DS, dissection, perforation

*For subjects with multiple lesions, the worst case of the multiple lesion characteristics will be used in the propensity score.

ARC-defined ST:

For the co-primary endpoint of ARC-defined (definite/probable) ST, the one-sided exact test for single proportion comparing the observed ARC ST rate of the test group to the pre-specified performance goal will be performed. Specifically, if the one-sided 97.5% upper confidence bound for the observed ARC ST rate of the test group is less than the performance goal, the test group will be considered to meet the performance goal.

12.1.2. Secondary Endpoint

The rate of bleeding, based upon the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5), between 3 and 15 month expressed as the proportion of subjects who experience bleeding between 3 and 15 months among all subjects who either experience bleeding between 3 and 15 months or survive free of bleeding for at least 425 days (analysis excludes subjects on chronic anticoagulants).

12.1.2.1. Hypothesis

The null hypothesis that the difference of bleeding rates between test group and historical control group is greater than or equal to zero will be tested against the alternative hypothesis that the difference between test group and historical control group is less than zero:

H_0: $P_{MB\text{-}3M} - P_{MB\text{-}12M} \geq 0$

H_1: $P_{MB\text{-}3M} - P_{MB\text{-}12M} < 0$

where $P_{MB\text{-}3M}$ and $P_{MB\text{-}12M}$ are the 3 to 15-month bleeding rates for the 3-month DAPT test group and the 12-month DAPT historical control group, respectively.

The historical control group for the hypothesis testing for bleeding is only from HCRI DAPT Study minus TAXUS. A second propensity score model will be developed based on the same set of covariates used in the propensity score model for the death/MI co-primary endpoint. The second propensity score model using quintile adjustment for the bleeding will be used to test the one-sided hypothesis of superiority of the test group compared to historical control group.

12.1.2.2. Sample Size

The expected rate of 4% for 3 to 15 month bleeding rate in subjects at high risk for bleeding for control group is estimated from the BSC PROMUS subjects enrolled in the HCRI DAPT study. The expected rate for 3 to 15 month bleeding rate in subjects at high risk for bleeding for test group is set to be 2.19%. In the control group, there are approximately 1,240 historical -limus DES high risk for bleeding subjects available from HCRI DAPT Study minus TAXUS. The number of evaluable subjects available in the test group required in the propensity score model for the death/MI co-primary endpoint and the ARC ST co-primary endpoint is 1,650. Given the number of subjects of 1,650 in the test group and 1,240 in the historical control group, the unadjusted power is 80%. Assuming that the dropout rate due to the ineligibility between 0 and 3 months for the test group is 15% and the expected attrition rate between 3 and 15 months is 3%, the study needs to enroll 2,000 subjects for the test group.

The enrollment may be terminated earlier if the observed dropout rate between 0 and 3 months is projected to be less than 15%. Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate in 0 to 3 months is projected to be >15%.

The sample size calculation is based on unequal allocation using 2-group chi-square test compare two proportions using nQuery Advisor® Version 5.0.

12.1.2.3. Statistical Methods

The second propensity score model with quintile adjustment will be used to address baseline imbalance between the test group and the historical control group. The null hypothesis will be tested against alternative hypothesis using the propensity score quintile adjusted secondary endpoint of bleeding for testing superiority between the test group and the historical control group.

The adjusted between-group difference estimate ($\bar{d}$) and the standard error ($SE(\bar{d})$) of the adjusted between-group difference will be used to construct the 97.5% upper confidence bound of the adjusted between-group difference using normal approximation to binomial. If the 97.5% upper confidence bound is less than zero, the null hypothesis will be rejected for the secondary endpoint of bleeding and the test group will be concluded to be superior to historical control group.

12.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.3 or later (Copyright© 2002-2010 by SAS Institute Inc., Cary, North Carolina, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific Statistical Analysis Plan.

12.2.1. Analysis Sets

For the EVOLVE Short DAPT Study, a subject is considered enrolled once an informed consent form has been signed and the subject has received at least one commercial SYNERGY stent. Enrolled subjects must meet all inclusion and no exclusion criteria. The analysis set for the test group includes enrolled subjects who meet criteria for discontinuation of P2Y12 inhibitor and who discontinue P2Y12 inhibitor at 3 months. The analysis set will be used as the test group in the propensity score model.

For the death/MI co-primary endpoint analysis, the EVOLVE Short DAPT-like high risk for bleeding subjects will be extracted from HCRI DAPT, PE+ PAS, and PE PROVE studies to form the historical control group. For the secondary bleeding endpoint analysis, the EVOLVE Short DAPT-like high risk for bleeding subjects will be extracted from HCRI DAPT study only to form the historical control group. Bleeding events were not adjudicated by the CEC in the PE+PAS or the PE-PROVE study.

The EVOLVE Short DAPT-like subjects are defined as subjects who meet the EVOLVE Short DAPT Study inclusion criteria and do not meet any of the following exclusion criteria at the time of the index procedure:

- indication for the index procedure of acute ST elevation MI (STEMI) or Non ST elevation MI (NSTEMI),
- previously treated with intravascular brachytherapy,
- left main target lesion,

- more than 3 lesions treated,
- more than 2 vessels treated,
- bifurcations,
- in-stent restenosis,
- saphenous vein graft,
- TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing, and
- thrombus or possible thrombus present in the target vessel (by visual estimate).

The high risk for bleeding subject set is defined as a set of subjects who meets one or more of the following criteria at the time of enrollment: ≥ 75 years of age and, in the opinion of the investigator, the risk of bleeding associated with >3 months of DAPT outweighs the benefit, chronic or lifelong anticoagulation therapy, history of major bleeding (severe/life threatening or moderate bleeding based on the GUSTO classification) within 12 months of the index procedure, stroke (ischemic and hemorrhagic), or renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent), and platelet count ≤100,000 μL.

12.2.2. Control of Systematic Error/Bias

An independent Clinical Events Committee (CEC) will review clinical events encountered during the study. The CEC will be blinded to the study center and subject identification to the extent possible.

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. The distribution of prognostic factors between subjects with and without data will be examined. 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 may be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be evaluated and values determined to be invalid will be queried. All data will be included in the analysis.

Propensity Scores Modeling Approach

To avoid potential bias, an independent propensity score model team, who is blinded to the outcome data, will develop two propensity score models based on the same set of covariates with three historical studies used in the first model and one historical study used in the second model.

The first propensity score model for the death/MI co-primary endpoint will be based on the analysis set for the test group from the EVOLVE Short DAPT Study and the EVOLVE Short DAPT-like high risk for bleeding subjects for the control group from HCRI DAPT, PE+ PAS, and PE PROVE studies.

The second propensity score model for bleeding will be based on the analysis set for the test group from the EVOLVE Short DAPT Study and the EVOLVE Short DAPT-like high risk for bleeding subjects for the control group from HCRI DAPT study. Subjects who were on long-term anticoagulation therapy and who were anticipated to still be on an anticoagulant at the time of randomization were not eligible for enrollment in HCRI DAPT study. In order to make a like-

to-like comparison between test and control groups, subjects with a need for chronic or lifelong anticoagulation therapy in the test group will be excluded from the second propensity score model for the bleeding secondary endpoint.

The independent propensity score model team will select the appropriate propensity score models prior to the endpoint analyses and file the propensity score baseline covariate modeling as an IDE supplement. The selected propensity score models will be delivered to an independent outcome reporting team for the endpoint analyses. The independent outcome reporting team will use these propensity score models to test the hypotheses of the test group compared to the control group and to compare other clinical outcomes between the test group and control group.

The missing data for the propensity score model covariates will be imputed. The within-study median value of the non-missing covariate for the subjects used in the propensity score model will be used as the imputed value for the missing continues covariate. The within-study mode value of the non-missing covariate for the subjects used in the propensity score model will be used as the imputed value for the missing discrete covariate.

12.2.3. Number of Subjects per Investigative Site

The maximum number of subjects to be enrolled per site is 200.

12.3. *Data Analyses*

Baseline data will be summarized by treatment group. Subject demographics, clinical history, risk factors, and pre-procedure lesion characteristics will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample).

The propensity score quintile adjusted baseline variables will be compared between the test group and control group. P-values will be provided using normal approximation.

12.3.1. Post-procedure Endpoints

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, n, minimum, maximum) and frequency tables or proportions for discrete variables.

12.3.2. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this trial early for study success. A data monitoring committee (DMC) will monitor the safety events for the purpose of stopping the trial for futility.

12.3.3. Subgroup Analyses

For the test subjects with 3-month DAPT, planned subgroup analyses will include gender (female/male), diabetic status (medically treated diabetics/non medically treated diabetics), number of lesions (single lesion/multiple lesions), number of vessels (single vs multiple vessels treatment), long lesion, stent model (small vessel, workhorse, and large vessel), region (US vs

OUS), 0-3 month P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor), DAPT Score (62) , or any subgroups identified in the univariate/multivariate model as significant predictors for co-primary endpoints and secondary endpoint.

12.3.4. Justification of Pooling

An assessment of the poolability of 3-month eligible subjects across sites will be performed based on:

1) the co-primary endpoint of all death/MI for the test group,

2) the co-primary endpoint of all death/MI for the control group,

3) the co-primary endpoint of ARC ST for the test group,

4) the secondary endpoint of bleeding for the test group, and

5) the secondary endpoint of bleeding for the control group

using logistic regression with site as a factor and co-primary endpoints as the outcome. Sites with fewer than 10 subjects enrolled will be combined into "virtual sites" based on geographic regions within United States, Europe, Japan, and Brazil, so that "virtual sites" have at least 10 subjects but no more than the largest enrolling site. If the two-sided P value for the site effect is ≥ 0.15, it will be concluded that the site effect is not different across sites, and the site data can be pooled. If the two-sided P value for site effect is <0.15, site differences will be explored.

The poolability assessment of the treatment-by-site interaction based on the common sites enrolling both the 3-month eligible test subjects and the historical control subjects will be performed:
1) the co-primary endpoint of all death/MI for the 3-month eligible test/control subjects and

2) the secondary endpoint of bleeding the 3-month eligible test/control subjects.

An assessment of the poolability of subjects across sites will be made using logistic regression with treatment, site and the interaction of site by treatment as independent variables and co-primary endpoints as the outcome. The same model will be assessed for the secondary endpoint as the outcome. Sites with fewer than 10 subjects enrolled will be combined into "virtual sites" based on geographic regions within United States, Europe, Japan, and Brazil, so that "virtual sites" have at least 10 subjects but no more than the largest enrolling site. If the two-sided P value for the interaction coefficient is ≥ 0.15, it will be concluded that the treatment effect is not different across sites, and the data can be pooled. If the two-sided P value for the interaction coefficient is <0.15, site differences will be explored.

12.3.5. Multivariate Analyses

Univariate and multivariate analyses may be performed to assess the effect of potential predictors on the co-primary endpoints and secondary endpoint using logistic regression as described in the Statistical Analysis Plan

12.3.6. Other Analyses

Data collected for the follow-up period of 3 to 15 months will be analyzed using appropriate univariate and multivariate models. Kaplan-Meier plots of time-to-event variables will be constructed. The Cox proportional hazards regression model will be used to assess the effects of risk factors on the time-to-event variables. Multivariate models will be used to assess the predictability of outcome from the risk factors.

12.3.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved before performing the analyses. 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 BSC 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 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 BSC 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 Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ISO 14155 or International Conference on Harmonization (ICH)/Good Clinical Practice (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 (at least 3 years in Japan) 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 pertinent individual country laws and regulations.

It is BSC's responsibility to inform the Investigator and site when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

In Japan, BSC must maintain necessary essential documents for 5 years from the date of the marketing application approval (or until completion of re-examination, if applicable and if longer than 5 years) or until 3 years have elapsed since the formal discontinuation of the clinical investigation of the device, whichever is longer.

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 and/or notifications (e.g., IRB/EC/regulatory body) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator should 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 protocol, 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, notification, site re-training, or discontinuation) will be put into place by the sponsor.

16. Device/Equipment Accountability

Device identification should be entered into the eCRF for all SYNERGY devices used.

Local procedures should be followed to return unused, expired, or malfunctioning commercial devices, if applicable.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155 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, Japan Medical Device GCP 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 center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the protocol, 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 Clinical Study Agreement and 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 center 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) every adverse event (as reportable per protocol) and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, 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.
- Allow BSC to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- 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 AEs, as described in the ICF.
- Inform the subject of the nature and possible cause of any AEs 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.
- 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 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, included but not limited to conducting the informed consent process, the 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/ Independent Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to BSC 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.

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.

A copy of the written IRB/EC and/or regulatory authority approval (if applicable) of the protocol (or permission to conduct the study) and ICF, must be received by BSC before recruitment of subjects into the study.

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 a 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.

BSC will keep subjects' health information confidential in accordance with all applicable laws and regulations. BSC 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's identifying data 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 study Monitoring Plan, to assess continued compliance with the current, approved protocol/amendment(s) and applicable regulations. In addition, the 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 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. The monitoring plan will include source data verification for an approximate sampling of 10% of subjects enrolled. A risk-based approach to source data verification will be implemented as described in the Monitoring Plan.

The 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 21.

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 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(63). 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. *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 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 (64-66). 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.

19.4. *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.

19.5. *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. Conversely, discontinuation of P2Y12 inhibitor may have additional risks, including stent thrombosis or myocardial infarction. There may be additional risks linked to the procedure which are unforeseen at this time.

19.6. *Possible Interactions with Concomitant Medical Treatments*

Refer to the SYNERGY DFU for information on known drug interactions with everolimus.

19.7. *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, adherence to eligibility criteria for discontinuation of P2Y12 inhibitor at 3-months, 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.

19.8. *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. A shortened duration of dual antiplatelet therapy after stent implantation may decrease the risk of bleeding. This clinical trial has been designed to investigate potential benefits of SYNERGY with a shortened duration of dual antiplatelet therapy.

19.9. *Risk to Benefit Rationale*

Evaluation of the risks and benefits that are expected to be associated with use of the SYNERGY stent demonstrate that when used under the conditions intended, the benefits associated with use of the SYNERGY stent should outweigh the risks and the SYNERGY stent is suitable for its intended purpose.

Based on the design feature of the SYNERGY stent (polymer resorption occurring soon after completion of drug release at 90 days), it is expected that treatment with 3 months of DAPT will be safe in the patient population defined by the study selection criteria and more specifically in patients at high risk for bleeding, and may result in benefits such as avoidance of additional bleeding, cost and delay of non-cardiac procedures relative to a strategy of longer-term DAPT in the setting of current durable polymer drug-eluting stents.

20. Safety Reporting

20.1. *Definitions and Classification*

All serious adverse events (SAE), adverse device effects (ADE), death, MI, TVR, stroke, stent thrombosis, as well as bleeding events will be collected from the start of the index procedure (sheath insertion) through the 15-month follow-up visit.

Adverse event definitions are provided in Table 20.1-1. Administrative edits were made on the definition of serious adverse event to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015) for clarification purposes.

Table 20.1-1: Adverse Event 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 (any procedure in the clinical investigation plan). 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 definition includes any adverse event resulting from insufficient or inadequate 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 from intentional misuse 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: • Led to death, • Led to serious deterioration in the health of the subject, as defined by either: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • 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 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) *Ref: 21 CFR 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 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.

Table 20.1-1: Adverse Event Definitions

Term	Definition
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 device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

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 a specific SAE (see Table 20.1-1 for AE definitions). Any AE that meets protocol reporting criteria experienced by the study subject after the start of the index procedure must be captured on the eCRF.

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

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate eCRF.

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

20.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device and procedure. See criteria in Table 20.2-1:

Table 20.2-1: Criteria for Assessing Relationship of Study Device and 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; 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 o the investigational device or procedures are applied to; o 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);

Table 20.2-1: Criteria for Assessing Relationship of Study Device and Procedure to Adverse Event

Classification	Description
	• 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.

20.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.3-1.

Table 20.3-1: 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[1] of the event. • Reporting required through the end of the study
	Provide source documentation (unidentified) as requested by the Sponsor	• When documentation is available
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide source documentation (unidentified) as requested by the Sponsor	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)	Complete Device Deficiency CRF with all available new and updated information	• Within 2 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study
Adverse Device Effect (Non-Serious)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information

1 The "become aware date" for an event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.

Abbreviations: AE=adverse event; CRF=case report form; eCRF=electronic case report form;

Table 20.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline

UADE=unanticipated adverse device effect

20.4. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. 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 to be reported as AEs. However, if there is an AE that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

Device deficiencies that did not lead to an AE but could have led to a SAE if:

- either suitable action had not been taken,
- intervention had not been made, or
- circumstances had been less fortunate,

should be reported per Table 20.3-1.

20.5. *Reporting to Regulatory Authorities /IRBs /IECs /Investigators*

BSC will notify all participating study sites 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/ECs, and regulatory authorities as applicable according to local reporting requirements.

Boston Scientific Corporation, Investigator, or Site must notify the IRB/EC of any UADEs, USADEs, SADEs, SAEs, device deficiencies, and other CEC events as applicable according to local reporting requirements (refer to Section 22.2.1 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.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study-required procedures and/or testing, or data collection. For subjects less than 20 years of age enrolled at a Japanese site, the subject and the subject's legal representative must provide written Informed Consent.

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

BSC 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 center's IRB/EC. Any modification requires approval 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 center 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 clinical site and a copy of the signed and dated document and any other written information must be given to the person signing the form. In Japan, signature can be replaced by printed name and seal of appropriate individuals.

Failure to obtain subject consent will be reported by BSC to applicable regulatory bodies according to their requirements. Any violations of the informed consent process must be reported as deviations to BSC 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, or

following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific Corporation approval is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine if the subject population is to be re-consented.

A Screening Log will be maintained to document select information about candidates who fail to meet the enrollment eligibility criteria, including, but not limited to, the reason for screen failure.

22. Committees

22.1. *Steering Committee*

A Steering Committee composed of BSC Clinical Management, the Global and Co-Principal Coordinating Investigators , and other investigators/physicians experienced in interventional cardiology will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

22.2. *Dynamic Safety Monitoring Committee*

To promote early detection of safety issues, BSC processes will provide accelerated evaluation of AEs. 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. During regularly scheduled monitoring visits, the clinical research monitors will support the dynamic reporting process through their review of source document information.

22.2.1. Clinical Events Committee

The Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise who review and adjudicate endpoint events 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 death, MI, stent thrombosis, bleeding, stroke, and target vessel revascularization.

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. Contact information for the CEC is included in the study Manual of Operations for Japanese sites.

22.2.2. Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for the oversight review of safety events. The DMC will include leading experts in cardiovascular interventional therapy, cardiovascular surgery, and biostatistics who are not participating in the study and who have no affiliation with

BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC 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.

- Significant new information (e.g. safety or product performance) which affects the decision to continue the study
- Withdrawal of FDA or other regulatory authority approval to conduct the clinical study
- A decision on the part of BSC 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 Short DAPT Study may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. 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 centers by BSC. 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 BSC.

In the event an Investigator terminates participation in the study, study responsibility will be transferred to a co-Investigator, if possible. In the event there are no opportunities to transfer Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Investigator must return all documents to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Center

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 center has multiple or severe protocol violations without justification and/or fails to follow remedial actions. The Principal Investigator at the site must make a provision for the continued medical monitoring of subjects that were enrolled in the study.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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. In accordance with the Corporate Policy for the Conduct of Human Subject Research, 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 Global and Co-Principal Coordinating Investigators and/or 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.

25. Reimbursement and Compensation for Subjects (Japan Only)

25.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

25.2. *Compensation for Subject's Health Injury*

In the event of clinical study-related health injury to a subject, Boston Scientific Japan (BSJ) will respond based on the clinical study agreement with the investigational site and BSJ work instruction

26. Bibliography

1. Thygesen K, Alpert JS, Jaffe AS et al. Third Universal Definition of Myocardial Infarction. Journal of the American College of Cardiology 2012;60:1581-1598.
2. Colombo A, Drzewiecki J, Banning A et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-94.
3. Ellis SG, Stone GW, Cox DA et al. Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). JACC Cardiovasc Interv 2009;2:1248-59.
4. Fajadet J, Wijns W, Laarman GJ et al. Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. EuroIntervention 2010;6:562-7.
5. Grube E, Silber S, Hauptmann KE et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38-42.
6. Kirtane AJ, Gupta A, Iyengar S et al. Safety and Efficacy of Drug-Eluting and Bare Metal Stents: Comprehensive Meta-Analysis of Randomized Trials and Observational Studies. Circulation 2009;119:3198-3206.
7. Meredith IT, Ormiston J, Whitbourn R et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. EuroIntervention 2005;1:157-64.
8. Morice MC, Serruys PW, Barragan P et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299-304.
9. Morice MC, Serruys PW, Sousa JE et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.
10. Moses JW, Leon MB, Popma JJ et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.
11. Serruys PW, Ong ATL, Piek JJ et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. EuroIntervention 2005;1:58-65.
12. Silber S, A. C, Banning AP et al. Final 5-Year Results of the TAXUS II Trial.A Randomized Study to Assess the Effectiveness of Slow- and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for De Novo Coronary Artery Lesions. Circulation 2009;120:1498-1504.
13. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989-97.
14. Stettler C, Wandel S, Allemann S et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937-48.

15. Stone GW, Ellis SG, Cox DA et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.
16. Tsuchida K, Piek JJ, Neumann FJ et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). EuroIntervention 2005;1:266-72.
17. Weisz G, Leon MB, Holmes DR, Jr. et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. J Am Coll Cardiol 2009;53:1488-97.
18. Wiemer M, Serruys PW, Miquel-Hebert K et al. Five-year long-term clinical follow-up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT FIRST trial. Catheter Cardiovasc Interv 2010;75:997-1003.
19. Kang SH, Park KW, Kang DY et al. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. Eur Heart J 2014;35:1147-58.
20. Palmerini T, Biondi-Zoccai G, Della Riva D et al. Clinical Outcomes With Bioabsorbable Polymer- Versus Durable Polymer-Based Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. Journal of the American College of Cardiology 2014;63:299-307.
21. Daemen J, Wenaweser P, Tsuchida K et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667-78.
22. Finn AV, Joner M, Nakazawa G et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435-41.
23. Kotani J, Awata M, Nanto S et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. J Am Coll Cardiol 2006;47:2108-11.
24. Nakazawa G, Nakano M, Otsuka F et al. Evaluation of polymer-based comparator drug-eluting stents using a rabbit model of iliac artery atherosclerosis. Circulation: Cardiovascular Interventions 2011;4:38-46.
25. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. Minerva Cardioangiologica 2009;57:567-84.
26. Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery DiseaseA Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2016:In press.
27. Wijns W, Kolh P, Danchin N et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501-55.
28. Mauri L, Kereiakes DJ, Yeh RW et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New Engl J Med 2014;371:2155-2166.
29. Abo-salem E, Alsidawi S, Jamali H, Effat M, Helmy T. Optimal duration of dual antiplatelet therapy after drug eluting stents: Meta-analysis of randomized trials. Cardiovascular Therapeutics 2015:n/a-n/a.

30. Cassese S, Byrne RA, Ndrepepa G, Schunkert H, Fusaro M, Kastrati A. Prolonged dual antiplatelet therapy after drug-eluting stenting: meta-analysis of randomized trials. Clin Res Cardiol 2015.
31. Giustino G, Baber U, Sartori S et al. Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American College of Cardiology 2015;65:1298-1310.
32. Navarese EP, Andreotti F, Schulze V et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ 2015;350:h1618-h1618.
33. Palmerini T, Benedetto U, Bacchi-Reggiani L et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. The Lancet 2015;385:2371-2382.
34. Meredith IT, Verheye S, Dubois CL et al. Primary endpoint results of the EVOLVE trial: A randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol 2012;59:1362-1370.
35. Wilson GJ, Marks A, Berg KJ et al. The SYNERGY biodegradable polymer everolimus eluting coronary stent: Porcine vascular compatibility and polymer safety study. Catheter Cardiovasc Interv 2015:[Epub ahead of print].
36. Meredith IT, Whitbourn R, Scott D et al. PLATINUM QCA: a prospective, multicentre study assessing clinical, angiographic, and intravascular ultrasound outcomes with the novel platinum chromium thin-strut PROMUS Element everolimus-eluting stent in de novo coronary stenoses. EuroIntervention 2011;7:84-90.
37. Stone GW, Teirstein PS, Meredith IT et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: The PLATINUM Trial. J Am Coll Cardiol 2011; 57:1700-1708.
38. Kereiakes D. Four-year results of the PLATINUM randomized trial: Can stent metal alloy composition and design affect late clinical outcomes? . 'Presented at:' ACC 2014; Washington, D.C.
39. Meredith IT, Teirstein PS, Bouchard A et al. Three-year results comparing platinum-chromium PROMUS Element and cobalt-chromium XIENCE V everolimus-eluting stents in de novo coronary artery narrowing (from the PLATINUM Trial). Am J Cardiol 2014;doi: 10.1016/j.amjcard.2013.12.011.
40. Meredith IT, Teirstein PS, Stone GW et al. Two-year results of the PLATINUM SV Trial: Evaluation of a 2.25mm platinum chromium everolimus-eluting stent in de novo coronary artery lesions. 'Presented at:' Euro PCR 2012; Paris.
41. Meredith IT, Teirstein PS, Stone GW et al. The PLATINUM Small Vessel trial: Evaluation of the novel thin-strut platinum-chromium PROMUS Element small vessel everolimus-eluting stent. 'Presented at:' EuroPCR 2011; Paris.
42. Stone GW. Two-year results of the PLATINUM randomized trial comparing platinum chromium PROMUS Element and cobalt chromium PROMUS/XIENCE V everolimus-eluting stents in de novo coronary artery lesions. 'Presented at:' ACC 2012; Chicago, IL, USA.
43. Stone GW. Final Five-Year Results of the PLATINUM Randomized Trial Comparing Platinum Chromium PROMUS Element and Cobalt Chromium PROMUS/XIENCE V Everolimus-Eluting Stents in Workhorse Lesions. 'Presented at:' ACC 2015; Chicago, IL.

44. Teirstein P. Two-year outcomes following implantation of 32mm and 38mm platinum chromium everolimus-eluting element stents in long coronary lesions. 'Presented at:' TCT 2012; Miami, FL.
45. Teirstein PS. Three-year results of the PLATINUM Small Vessel and Long Lesion trials evaluating the platinum chromium everolimus-eluting stent in de novo coronary artery lesions. 'Presented at:' TCT 2013; San Francisco, CA, USA.
46. Teirstein PS. Four-Year Outcomes Following Implantation of the Promus Element® Platinum Chromium Everolimus-Eluting Stent in De Novo Coronary Artery Lesions in Small Vessels and Long Lesions: Results of the PLATINUM Small Vessel and Long Lesion Trials. 'Presented at:' TCT 2014; Washington, DC.
47. Teirstein PS, Meredith IT, Feldman RL et al. Two-year safety and effectiveness of the platinum chromium everolimus-eluting stent for the treatment of small vessels and longer lesions. Catheterization and Cardiovascular Interventions 2015;85:207-215.
48. Teirstein PS, Stone GW, Meredith IT et al. Platinum Chromium Everolimus-Eluting Stent in Long Coronary Lesions. 'Presented at:' TCT 2011; San Francisco.
49. Saito S, Iwabuchi M, Muramatsu T et al. Two-Year Outcomes Following Platinum Chromium Everolimus-Eluting Stent Implantation in Small Vessel Lesions in Japan. 'Presented at:' Cardiovascular Revascularization Therapeutics;2013; 2013.
50. Saito S, Iwabuchi M, Muramatsu T et al. PLATINUM Japan SV: Platinum Chromium Everolimus-Eluting Stent in Small Vessels. 'Presented at:' Cardiovascular Revascularization Therapeutics 2012.
51. Gao R, Han Y, Yang Y et al. PLATINUM China: A prospective, randomized investigation of the platinum chromium everolimus-eluting stent in de novo coronary artery lesions. Catheterization and Cardiovascular Interventions 2015;85:716-723.
52. Meredith IT, Verheye S, Weissman NJ et al. Six-month IVUS and two-year clinical outcomes in the EVOLVE FHU trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. EuroIntervention 2013;9:308-15.
53. Verheye S. Six-Month IVUS and 12-Month Clinical Outcomes in the EVOLVE FHU Trial: A Randomized Evaluation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Stent. 'Presented at:' EuroPCR 2012; Paris, France.
54. Meredith IT. Four-year clinical outcomes in the EVOLVE trial: A randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. 'Presented at:' EuroPCR 2015; Paris, France.
55. Meredith IT. Three-year clinical outcomes in the EVOLVE FHU trial: A randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. 'Presented at:' EuroPCR 2014; Paris, France.
56. Kereiakes DJ, Meredith IT, Windecker S et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. Circ Cardiovasc Interv 2015;8:e002372.
57. Windecker S. Primary Clinical Outcomes of the EVOLVE II Diabetes Substudy Evaluating a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent in Diabetic Patients. 'Presented at:' EuroPCR 2015; Paris, France.
58. Meredith IT. Nine-month Primary Endpoint Results of the EVOLVE II QCA Study: A Prospective, Multicenter Trial Assessing Clinical, Angiographic, and IVUS Outcomes with the Novel Platinum-Chromium Abluminally-coated Bioabsorbable Polymer

SYNERGY Everolimus-Eluting Stent in De Novo Coronary Stenoses. 'Presented at:' ACC 2015; Chicago, IL.
59. Mehran R, Rao SV, Bhatt DL et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. Circulation 2011;123:2736-2747.
60. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med 1993;329:673-82.
61. Rao AK, Pratt C, Berke A et al. 37th Annual Scientific SessionThrombolysis in myocardial infarction (TIMI) trial—Phase I: Hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. Journal of the American College of Cardiology 1988;11:1-11.
62. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-1749.
63. Directions for Use, SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System.
64. Dani S, Kukreja N, Parikh P et al. Biodegradable-polymer-based, sirolimus-eluting Supralimus stent: 6-month angiographic and 30-month clinical follow-up results from the series I prospective study. EuroIntervention 2008;4:59-63.
65. Ormiston JA, Abizaid A, Spertus J et al. Six-month results of the NEVO Res-Elution I (NEVO RES-I) trial: a randomized, multicenter comparison of the NEVO sirolimus-eluting coronary stent with the TAXUS Liberte paclitaxel-eluting stent in de novo native coronary artery lesions. Circ Cardiovasc Interv 2010;3:556-64.
66. Vedat A, Selcuk G, Refik E et al. Treatment of patients with coronary artery disease with biodegradable polymer based paclitaxel-eluting Infinnium coronary stent system: results of 1-year clinical follow-up a single center experience. Indian Heart J 2009;61:254-7.

27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 27.1-1.

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ADE	adverse device effect
AE	adverse event
AHA	American Heart Association
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
BSC	Boston Scientific Corporation
BMS	bare metal stent
CABG	coronary artery bypass graft
CEC	Clinical Events Committee
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
EC	Ethics Committee
ECG	Electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
FHU	First Human Use
GCP	Good Clinical Practices
GUSTO	Global Strategies for Opening Occluded Coronary Arteries
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
ISO	International Standards Organization
ITT	intention to treat
IVUS	intravascular ultrasound
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LCX	left circumflex coronary artery
LL	long lesion
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
MACCE	major adverse cardiac and cerebrovascular event
MI	myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	Non ST elevation myocardial infarction
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
ST	Stent thrombosis
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
USADE	uanticipated serious adverse device effect

Table 27.1-1: Abbreviations

Abbreviation/Acronym	Term
ULN	upper limit of normal
URL	upper reference limit
US	United States
WH	Workhorse

27.2. ***Definitions***

ADVERSE DEVICE EFFECT (*Ref: ISO 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015)*

Adverse event related to the use of an investigational medical device.

***Note*:** This definition includes AEs resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

***Note*:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

ADVERSE EVENT (*Ref: ISO 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015)*

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

- The investigational medical device or comparator
- The procedures involved (study-required)

***Note*:** For users/other persons, this definition is restricted to events related to the investigational medical device

ADVERSE EVENT RELATIONSHIP TERMS

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;
- 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.

ANTICIPATED EVENT

Event that is previously identified in the protocol, ICF, or DFU

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.

BLEEDING CLASSIFICATIONS-GUSTO (60)

Major Bleeding will be defined by the GUSTO classification of "Severe/life-threatening" or "Moderate" below:

- 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

Bleeding events that are medically important, but that do not meet the severe/moderate levels (e.g., require laboratory testing, evaluation by a physician, ER visit, or cessation of either study medication or other antithrombotic therapies) will be collected.

BLEEDING CLASSIFICATIONS-Bleeding Academic Research Consortium (BARC) (59)

- Type 0: No Bleeding
- Type 1: Bleeding that is not actionable and does not cause the patient to seek treatment
- Type 2: Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
- Type 3a: Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding
- Type 3b: Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents
- Type 3c: Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
- Type 4: CABG-related bleeding within 48 hours
- Type 5a: Probable fatal bleeding
- Type 5b: Definite fatal bleeding

BARC types 2, 3a, 3b, 3c, 4, 5a and 5b will be collected in the study.

BLEEDING CLASSIFICATIONS-TIMI (61)

Non-CABG related bleeding

Major

- Any intracranial bleeding (excluding microhemorrhages 10 mm evident only on gradient-echo MRI)
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of 5 g/dL
- Fatal bleeding (bleeding that directly results in death within 7 d)

Minor

- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to 5 g/dL
- Requiring medical attention
- Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
- Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
- Leading to or prolonging hospitalization
- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Minimal

- Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG

- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of 5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output 2 L within a 24-h period

All TIMI bleeding events (with the exception of minimal) will be collected in this study.

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.

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.

DEATH

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

- Cardiac death: Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment.
- Vascular death: Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
- Non-cardiac death: Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

DEVICE DEFICIENCY (*Ref: ISO 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015)*

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

***Note**:* Device deficiencies include malfunctions, use errors, and inadequate labeling.

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.

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.

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.

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.
    - B1 lesion has one of the above characteristics
    - B2 lesion has two or more of the above characteristics
- 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 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 Short DAPT Study, the ramus will be considered to be a branch of the LCX for purposes of determining eligibility and for determining TVR.

MULTI-VESSEL DISEASE

Multi-vessel disease refers to the presence of >50% diameter stenosis in 2 or 3 major epicardial coronary vessels or bypassed branches.

MYOCARDIAL INFARCTION -3rd Universal Definition (1)

Spontaneous MI:

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

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

Percutaneous Coronary Intervention-Related Myocardial Infarction

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

AND

One of the following:

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

Coronary Artery Bypass Grafting-Related Myocardial Infarction

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

AND

One of the following:

- New pathological Q waves or new LBBB
- Angiographic documented new graft or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac marker values would be increased.

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

RESTENOSED LESION

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

RESTENOSIS

A > 50% reduction in diameter of a previously-treated lesion when compared to the reference luminal diameter.

SERIOUS ADVERSE DEVICE EFFECT (*Ref: ISO 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015)*

Adverse device effect that has resulted in any of the consequences characteristic of a SAE.

SERIOUS ADVERSE EVENT (*Ref: ISO 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015)*

Adverse event that:

- Led to death
- Led to a serious deterioration in the health of the subject as defined by either:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization of existing hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
- Led to fetal distress fetal death or a congenital abnormality or birth defect

STENT THROMBOSIS (8)

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 5mm 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 5mm 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

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)

STAGED PROCEDURE

Any elective percutaneous intervention using a SYNERGY stent that is not within a target vessel or any side branch of a target vessel treated during the index procedure and occurs ≤ 7 days after the index procedure.

TARGET LESION

Any lesion treated or attempted to be treated with a SYNERGY stent during the index or staged procedure(s). The target lesion includes the arterial segment treated with the stent plus the arterial segment 5 mm proximal and 5 mm distal to the treatment site.

TARGET LESION REVASCULARIZATION

A target vessel revascularization that involves a target lesion.

TARGET VESSEL

A target vessel is defined as any vessel containing a target lesion.

TARGET VESSEL FAILURE

Target vessel failure is defined as the composite of target vessel revascularization, cardiac death or target vessel related myocardial infarction

For the purposes of this protocol, if it cannot be determined with certainty whether MI was related to the target vessel it will be considered TVF.

TARGET VESSEL REVASCULARIZATION

Any attempted or successfully completed percutaneous or surgical revascularization of a target vessel.

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 14155-2011, MEDDEV 2.7/3 Revision 3, 5/2015*)

A 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.

28. Appendices

28.1. *Clinical Trial Organization (Japan)*

Clinical trial organization in Japan including CRO information, and a list of study sites in Japan is provided as an attachment only in Japan to fulfill local requirements

28.2. *Revision History*

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA to AB	November 13, 2015	Synopsis, Section 7, 12	Revision to include the rate of ARC Stent Thrombosis as a co-primary endpoint, rather than a secondary endpoint	FDA recommendation
AA to AB	November 13, 2015	Synopsis, Section 9.2	Revision to inclusion criteria defining subjects at high risk for bleeding	FDA recommendation
AA to AB	November 13, 2015	Synopsis, Section 9.3	Revision to exclusion criterion for NSTEMI	FDA recommendation
AA to AB	November 13, 2015	Synopsis, Section 11.10.1.2	Clarification of method to be used to assess DAPT compliance	FDA recommendation
AA to AB	November 13, 2015	Section 12.2.1	Revision to the analysis set definition to “enrolled subjects who are eligible for P2Y12 inhibitor discontinuation and discontinue the P2Y12 inhibitor at the 3 month assessment visit”	FDA recommendation
AA to AB	November 13, 2015	Synopsis, Section 7.3	Inclusion of rate of target lesion revascularization as an additional endpoint	Endpoint of interest
AA to AB	November 13, 2015	Table 12.1 1	Revision to propensity score covariates	FDA recommendation
AA to AB	November 13, 2015	N/A	Additional minor corrections/clarifications	Improve clarity of document

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AB to AC	November 17, 2015	Synopsis, Section 7.3	Additional Endpoint added "Rate of MI (Q-wave and non Q-wave, ST-related and not ST-related)"	Endpoint of interest
AB to AC	November 17, 2015	Section 11.4.1	Revision to recommended peri-procedural loading dose of clopidogrel from 600mg to ≥300mg	Lower recommended loading dose, as enrolled subjects are at higher risk for bleeding
AB to AC	November 17, 2015	Section 24	Addition of "Global and Co-Principal" to "BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Global and Co-Principal Coordinating Investigator(s) and/or Executive/Steering Committee at the onset of the project."	Clarification of role of Global and Co-Principal Coordinating Investigators in the Publication Process
AC to AD	June 20, 2016	Synopsis, Section 8.1	Update in planned # sites from "up to 110" to "up to 120"	Option of additional sites in protocol allows opportunity for enrollment projection, as needed
AC to AD	June 20, 2016	Synopsis, Section 7.2, Section 12.1.2	Secondary Endpoint of "Rate of major bleeding (GUSTO severe/life-threatening + moderate) between 3 and 15 month " revised to "Rate of bleeding, based upon	Modification to bleeding secondary endpoint to use the BARC classification and to remove subjects on chronic anticoagulants (higher risk for bleeding and not

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			the Bleeding Academic Research Consortium (BARC) classification (types 2, 3 and 5) between 3 and 15 months in subjects not taking chronic anticoagulation.	represented in the DAPT Study control population).
AC to AD	June 20, 2016	Synopsis, Section 11.10	Update to calculation for follow-up windows after 3-months. Windows for 6, 12 and 15 month follow-ups based upon the date of the 3-month visit (representing the date of DAPT discontinuation).	Revisions to allow full year of follow-up in analysis dataset, following the 3-month DAPT discontinuation. Removal of earlier half of 15-month visit ensures full year of follow-up after 3-month visit date.
AC to AD	June 20, 2016	Synopsis, Section 11.8	Addition of "• Enrolled subjects with a need for chronic or lifelong anticoagulation must be treated with a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure, but are not required to take aspirin in addition to the P2Y12 inhibitor between 0-3 months. These subjects may be treated with aspirin between 0-3 months, in addition to the	Clarification of antiplatelet requirements for subjects who are also taking chronic anticoagulants

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			P2Y12 inhibitor and anticoagulant at the discretion of the treating physician, but this is not required. • Enrolled subjects who are not on chronic anticoagulation must take both aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for 3 months following the index procedure. • Enrolled subjects will be evaluated at 3 months to confirm that discontinuation of P2Y12 inhibitor remains appropriate. • Subjects who are eligible for discontinuation of P2Y12 inhibitor therapy at 3 months, regardless of whether they are taking chronic anticoagulation, are required to take aspirin starting at 3 months and continuing for the duration of the study."	
AC to AD	June 20, 2016	Synopsis, Section 9.2	Revision to Inclusion from "Subject must be able to take study	Inclusion criterion revised to accommodate revised

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			required dual antiplatelet therapy (3 months of P2Y12 inhibitor, 15 months of aspirin)" to "Subject must be able to take study required dual antiplatelet therapy (as required per protocol)."	antiplatelet requirements for subjects taking chronic anticoagulants
AC to AD	June 20, 2016	Synopsis, Section 9.3, Section 12.2.1	Revision of exclusion criterion from "Planned treatment of more than 2 lesions" to "Planned treatment of more than 3 lesions."	Revision to align exclusion criterion with pivotal study for SYNERGY
AC to AD	June 20, 2016	Synopsis, Section 9.3, Section 12.2.1	Addition of exclusion criterion "Planned treatment of lesions in more than 2 major epicardial vessels"	Revision to align exclusion criterion with pivotal study for SYNERGY
AC to AD	June 20, 2016	Synopsis, Section 9.3	Revision of two exclusion criteria "Target lesion(s) treated during the index procedure that involves a side branch ≥ 2.0 mm in diameter by visual estimate" and "Target lesion(s) treated during the index procedure that involves a clinically significant side branch < 2.0 mm in diameter by visual estimate that has a clinically significant stenosis at the	Revision to align exclusion criterion with pivotal study for SYNERGY

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			ostium," to "Target lesion(s) treated that involves a complex bifurcation (i.e. bifurcation lesion requiring treatment with more than one stent)."	
AC to AD	June 20, 2016	Synopsis, Section 11.9	Additional language regarding staged procedures: "• A staged procedure is only permitted when all enrollment inclusion criteria and no enrollment exclusion criteria are met for all lesions treated during both the initial procedure and the subsequent staged procedure. • The total number of lesions treated during the index and staged procedures combined must not exceed 3. • The total number of epicardial vessels treated during the index and staged procedures combined must not exceed 2. • In the case of a staged procedure meeting these criteria, the subject should return for the 3-month visit (i.e. assessment for	Clarification of staged procedure requirements

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			eligibility to discontinue P2Y12 inhibitor) 90 days following the staged procedure + 30 days or - 7 days."	
AC to AD	June 20, 2016	Synopsis, Section 11.10	Addition of the following note: "(Note: Subjects taking chronic anticoagulation between 0-3 months are not eligible if they were not taking P2Y12 inhibitor or P2Y12 inhibitor/aspirin between 0-3 months)."	Clarification of eligibility of subjects on chronic anticoagulants for discontinuation of P2Y12 inhibitor at 3-months
AC to AD	June 20, 2016	Synopsis, Section 11.4, Section 11.10	Significant interruption of P2Y12 inhibitor or aspirin defined as 3 days or greater.	Clarification of reporting requirements for antiplatelet interruption.
AC to AD	June 20, 2016	Section 4	DAPT Guideline reference updated to "The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiographic Intervention recommends that, following DES implantation, patients with stable ischemic heart disease should receive clopidogrel (or an alternative	Revision to align with "ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease" (revised 2016).

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			P2Y12 inhibitor) in addition to aspirin for a minimum of 6 months, unless there is a high bleeding risk. Following DES implantation, patients with stable ischemic heart disease who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable."	
AC to AD	June 20, 2016	Section 10.1	Addition of "Enrollment should occur within 3 calendar days of the index procedure date."	Clarification of timeline for enrollment
AC to AD	June 20, 2016	Section 18	Removal of "and source data verification of all endpoint events (death, myocardial infarction, target vessel revascularization, stent thrombosis,	Detailed review of CEC events against source data will be performed by the Safety Function, rather than the on-site Clinical Research Associate.

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			stroke, and major bleeding)."	
AC to AD	June 20, 2016	Section 20.1, Definitions	References to MEDDEV updated	Update to align with recent revision (MEDDEV 2.7/3 Revision 3, 5/2015)
AC to AD	June 20, 2016	Section 20.1, Definitions	Serious Adverse Event definition: replaced "Led to serious deterioration in the health of the subject, that either resulted in…" with "Led to serious deterioration in the health of the subject, as defined by either…"	Clarification of definition
AC to AD	June 20, 2016	Section 20.2	Update of Criteria for Assessing Relationship of Study Device and Procedure to Adverse Event from "Unrelated and Related" to "Not Related, Unlikely Related, Possibly Related, Probably Related and Causal Relationship."	Update to align with recent revision (MEDDEV 2.7/3 Revision 3, 5/2015)
AC to AD	June 20, 2016	Section 22.1	Addition of "A Steering Committee composed of BSC Clinical Management, the Study Coordinating Principal Investigators, and other	Steering Committee has been convened for this study

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			investigators/physicians experienced in interventional cardiology will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission."	
AD to AE	April 4, 2017	Synopsis, Section 8.1, Section 12	# Subjects: Changed "approximately 2,000 subjects" to "up to 2,250 subjects." Addition of the following text: "Enrollment may be continued beyond 2,000 subjects (up to a maximum of 2,250 subjects) if the observed dropout rate	Increase maximum enrollment from "approximately 2,000 subjects" to "up to 2,250 subjects," to account for a slightly higher attrition rate of subjects not discontinuing from P2Y12 inhibitor at 3-months.

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
			in 0 to 3 months is projected to be >15%."	
AD to AE	April 4, 2017	Synopsis, Section 9.2 & 9.3	Removal of the following from Inclusion Criterion #1: "Need for chronic or lifelong anticoagulation therapy." Addition of the following Exclusion Criterion: "Subject who is taking (or is planning to take) chronic or lifelong anticoagulation within 15 months following index procedure." In addition, text throughout the protocol regarding antiplatelet requirements was removed/edited, given the new exclusion of this population.	This change will cap subset enrollment (subjects on anticoagulation) by removing from inclusion criterion (high risk bleeding qualifier) and adding it to the exclusion criteria. There has been a higher enrollment of patients on anticoagulation than expected and a cap is necessary to ensure comparability to the control population.