HONORHEALTH™

Research Institute

SYNIVUS-DAPT

SYNergy™ Stent System Implantation with Mandatory Intra-Vascular Ultra-Sound Guidance to Examine the Safety of Cessation of Dual Anti-Platelet Therapy in High Bleeding Risk Patients at One Month

National Clinical Trial (NCT) Identified Number: NCT03606642

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IDE Sponsor: David G. Rizik, MD

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Table of Contents

STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	SYNERGY™ Stent System Implantation with mandatory Intra-Vascular Ultra-Sound Guidance to Examine the Safety of Cessation of Dual Anti-Platelet Therapy in High Bleeding Risk Patients One Month (SYNIVUS-DAPT)
Study Description:	This is a prospective multicenter single-arm study designed to characterize the safety of 1 month of dual antiplatelet therapy (DAPT) in a patient population who are at increased risk for bleeding who are undergoing iLab IVUS-guided percutaneous coronary intervention (PCI) with a SYNERGY Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY™ Stent System). We hypothesize that the 1 to 13 month rates of Cardiac Death or Myocardial Infarction (SCAI definition), and Stent thrombosis after Boston Scientific IVUS-guided SYNERGY™ Stents implantation will be low and provide key hypothesis generating information to inform future larger-scale clinical studies
Objectives:	Primary Objectives: To determine the safety of 1-month DAPT in a High Bleeding Risk (HBR) patient population who are undergoing SYNERGY™ stent implantation.
Endpoints:	Primary Endpoint: • Rate of cardiac death or myocardial infarction (SCAI definition) from 1 to 13 months post-index procedure in the “as treated” (eligible for 30 day DAPT cessation) population.

Secondary Endpoints

- Rate of cardiac death or myocardial infarction (SCAI definition) from 1 to 13 months post-index procedure in the overall enrolled "intent-to-treat" patient population

- Rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) involving SYNERGY ™Stents from 1 to 13 months post-index procedure
- Rate of major bleeding (GUSTO severe/life threatening + moderate) from 1 to 13 months post-index procedure
- Ischemia-Driven (ID) Target Lesion Revascularization,
- ID Target Vessel Revascularization,
- Target Lesion Failure,
- Target Vessel Failure,
- All-Cause Death, and
- All-Cause Death or MI.

Study Population: Approximately 100 evaluable patients will be enrolled in this study with the possibility to expand enrollment to two hundred thirty one (231).

General 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 >1 months of DAPT outweighs the benefit,
   - Need for 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,
   - History of stroke (ischemic or hemorrhagic),
   - Renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent),
   - Platelet count ≥20,000/µL to ≤100,000/µL
   - In the opinion of investigator, patient is at significant risk of falling
   - Patient abuses drugs or alcohol
   - Hemoglobin ≤11.0 u/dl
2. Subject must be 18 years of age
3. Subject must be able to take study required dual antiplatelet therapy (1 month of P2Y12 inhibitor and aspirin, 13 months of antiplatelet monotherapy)

4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at the 1-month milestone if eligible per protocol
5. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific procedures are performed

Angiographic Inclusion Criteria

1. Subject must have had implantation of at least one SYNERGY™ Stent and the use of Boston Scientific IVUS for guided stent implantation
2. All implanted stents must be post dilated and must meet the following IVUS success criteria:
    a) Treated lesions in which the stent cross sectional area exceeds the distal reference cross sectional area
    b) If the stent cross sectional area is less than the distal reference cross sectional area additional post-dilatation must be performed, followed by repeat IVUS.
    c) Above IVUS criteria must be met after the 2nd post dilatation

    Note: if the IVUS criteria is not met after the 2nd post dilatation the patient is excluded
3. Stent procedure performed by an approved investigator
4. Vessel diameter ≥ 2.25 mm and ≤ 4.0 mm and lesion length ≤ 34mm
5. Pre-dilatation is up to the discretion of the investigator

General Exclusion criteria:

1. Subject with an indication for the index procedure of acute ST elevation MI (STEMI)
2. Subject with an indication for the index procedure of Non ST elevation MI (NSTEMI), based on the 3rd Universal MI definition
3. Subject with treatment with another coronary stent, other than a SYNERGY™ stent during the index procedure
4. Subject with a planned staged procedure > 7 days following the index procedure. (Note: Planned staged procedures are allowed if performed within 7 days of the index procedure and only when SYNERGY™ stents are used for both the index and staged procedures). Discontinuation of DAPT should occur 1 month after the last PCI procedure is completed
5. A staged procedure cannot be in a 3rd epicardial vessel if 2 epicardial vessels were treated during the index procedure
6. Subject has a known allergy to:
    - Contrast (that cannot be adequately pre-medicated)

- SYNERGY™ Stent system (e.g., everolimus. structurally related compounds, polymer or individual components) or
- Protocol-required concomitant medications(all P2Y12 inhibitors and aspirin)

7. Subject previously treated at any time with intravascular brachytherapy
8. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding
9. 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)
10. Subject intends to participate in an investigational drug or device clinical trial within 12 months following the index procedure (Note: registry, observational, data collection studies are not exclusionary)
11. Subject is judged inappropriate for discontinuation from P2Y12 inhibitor use at 1 month, due to another condition requiring chronic P2Y12 inhibitor use
    - If at the 30 day visit the patient has had a peri-procedural NSTEMI with an enzyme elevation >5% of the upper 99th percentile of either CK-MB or Troponin, the subject should not be taken off DAPT.
12. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within (≤)1 month following index procedure
13. Subject is a woman who is pregnant or nursing
14. Subject with a current medical condition with a life expectancy of less than 12 months
15. Subject with implantation of a drug-eluting stent other than SYNERGY™ Stents within 11 months prior to index procedure
16. Have been previously consented for this trial and screen failed
17. Any other clinically significant comorbidities, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks.

Angiographic Exclusion Criteria

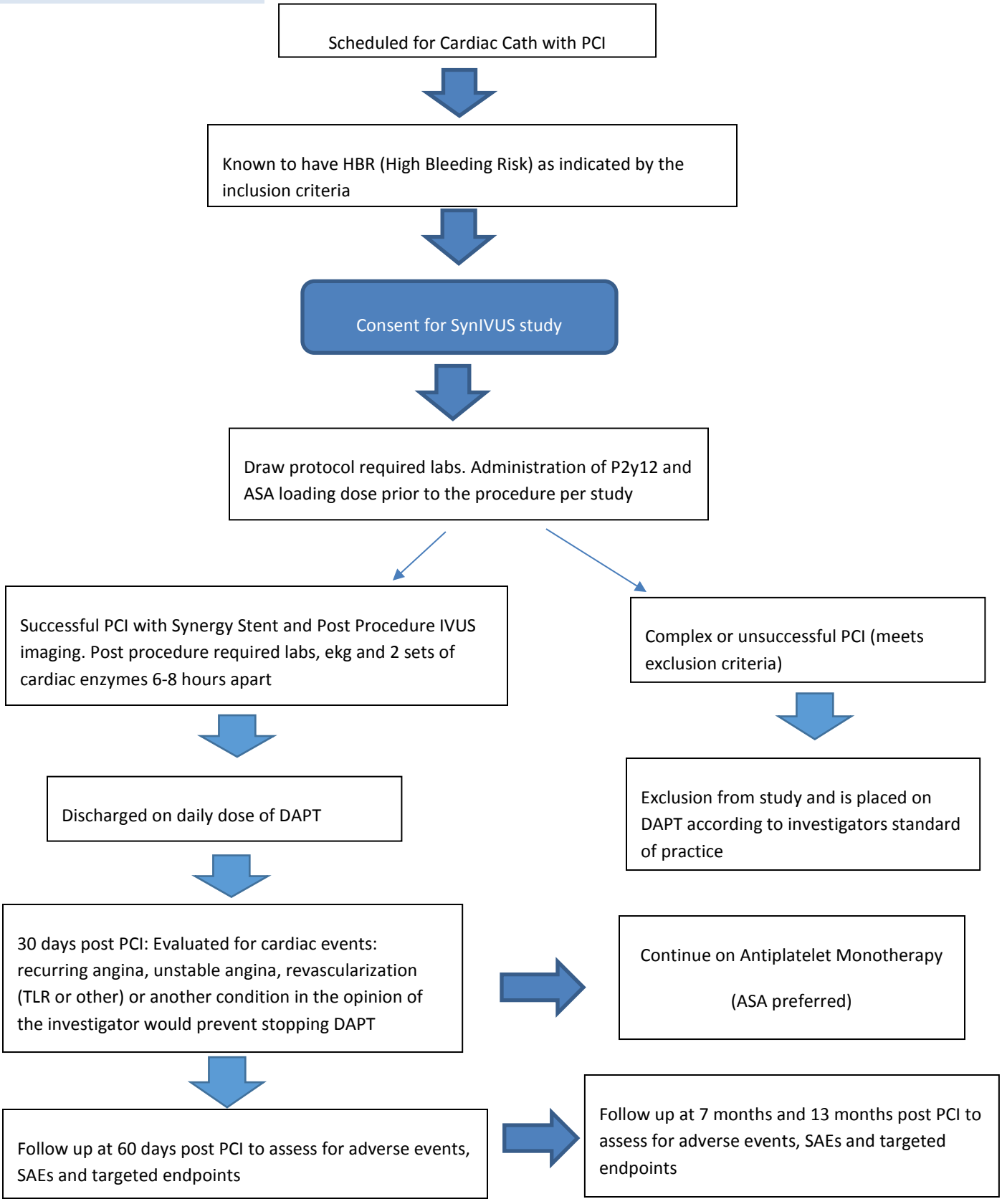
1. Target lesion(s) is located within a saphenous vein graft or an arterial graft
2. TIMI flow 0 (total occlusion)
3. Target lesion(s) is located in the left main

4. Potential Target lesion(s) that involve a complex bifurcation (i.e. bifurcation lesion requiring treatment with more than one stent)
5. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)
6. Patients requiring a treatment of more than two native epicardial vessels
7. More than three lesions in two epicardial vessels unless they can be covered by one stent.
8. In-stent restenosis of target lesion
9. Treatment of non-target lesions or lesions not treated with a Synergy™ stent
10. Subject who did not receive Boston Scientific IVUS guided stent implantation and assessment
11. Any target lesion that has not been post dilated and has not had post dilatation IVUS
12. Patients who do not meet the following IVUS success criteria:
    - Target lesion(s) in which the stent cross sectional area is less than the distal reference cross sectional area and additional post-dilatation is not performed, followed by repeat IVUS.
      ** Note: If the IVUS criteria is not met after the 2nd post dilatation the patient is excluded

Phase	**Pilot**
Description of Sites/Facilities Enrolling Participants:	The study will be conducted at HonorHealth System within the Phoenix, Arizona metropolitan area, and two institutions outside of the HonorHealth System. All Institutions within the HonorHealth system will collectively be considered a single "site". All sites have recognized expertise with Boston Scientific IVUS guided stent implantation and will use IVUS to perform the procedures. The study will not be conducted outside the United States and its territories. Additional sites may be added pending enrollment rates.
Description of Study Intervention:	This is a study designed to follow patients whom have received IVUS-guided Implantation of the SYNERGY™ Stents and discontinued DAPT at 1 month.
Study Duration:	24 Months
Participant Duration:	13 Months

Total Number of Patients: 231

1.2 STUDY DESIGN



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening/ Baseline[a]**	**Index Procedure (Day 1)**	**Post-Index Procedure[b] (Prior to discharge)**	**30 Days (+ 7 days Post PCI)** (in office)	**60 days (±7 days) Post PCI** (In office or via phone)	**7 months (±14 days[i]) Post PCI** (In office or via phone)	**13 Months (± 30 days[j]) Post PCI** (In office or via phone)
Informed Consent	X						
H&P[c]	X						
CBC w Diff, platelets	X		X				
BMP	X		X				
PT/INR (only if on warfarin, liver disease or severe anemia	X		X				
CPK, CK-MB or Troponin-I	X		X[d]				
EKG	X		X				
ConMeds (Only Cardiac	X		X	X	X	X	X
Cardiac Cath w PCI		X					
ASA LD	X[e]						
ASA MD		X[f]		X		X	X
P2Y12 LD		X[g]					
P2Y12 MD			X[h]	X		X	X
AE assessment		X	X	X	X	X	X
Angina assessment [k]				X	X	X	X
Angina Questionnaire				X			
EDC Completion	X	X	X	X	X	X	X

[a] to be completed ≤ 7 days prior to Index procedure
[b] To be completed within 24 hours after Index procedure
[c] Determination of high risk of bleeding (HRB)
[d] Perform 2, 6-8 hours apart, if cardiac enzyme levels are elevated (i.e. exceed the upper limits of normal as defined by local guidelines), serial measurements be performed until a decline is noted. If same day discharge draw one set immediately post PCI then 2nd set @ 6-8 hours after
[e] Aspirin loading dose (LD) = 325 mg. Start day of procedure (if not on chronic ASA)
[f] Aspirin maintenance dose (MD) = 81 mg. Start the day after aspirin loading dose
[g] P2Y12 Inhibitor Loading Dose (investigator preference): clopidogrel 600 mg PO x 1 or 75 mg PO daily x 4; prasugrel 60 mg PO x 1; ticagrelor 180 mg PO x 1. Start within 7 days of procedure.
[h] P2Y12 Inhibitor Maintenance Dose (investigator preference): clopidogrel 75 mg PO daily; prasugrel 10 mg PO daily; ticagrelor 90 mg PO BID. Start day after P2Y12 inhibitor loading dose
[i] 6 months post DAPT cessation
[j] 12 months post DAPT cessation
[k] Angina Assessment only at 60 days, 7 months and 13 months

2 INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to examine whether discontinuation of Dual Anti-platelet Therapy (DAPT) at 1 month after IVUS-guided implantation of the SYNERGY™Stent is feasible.

2.2 BACKGROUND

Numerous preclinical studies have shown enhanced healing and reduced inflammation with the 3rd generation SYNERGY™ Stents relative to second generation Permanent Polymer DES[1, 2, and 3]. Optical Coherence Tomography (OCT) findings suggest complete or near-complete endothelialization of the SYNERGY™ Stent at 1, 2, and 3 months[4,5,6]. Mounting clinical evidence suggests a favorable safety and efficacy profile in selected patient populations[7,8], real-world patient populations[9,10], complex patients where DAPT has been discontinued at 3-months[11] and elderly patients (over 74 years of age) in which DAPT was discontinued at 1 month. Of particular note for the group of elderly patients studied with 1 month DAPT discontinuation is that no patient who received a SYNERGY stent implant experienced a Stent Thrombosis after discontinuing DAPT at 1 month.[12]

Additionally, numerous studies have demonstrated the benefit of IVUS-guided implantation of coronary stents[13,14] in terms of the safety and efficacy benefits.

The goal of this study would be to combine the pro-healing design features of the SYNERGY™ Stents with a known procedural predictor of good outcomes (IVUS) and test the two in combination in an environment where dual antiplatelet therapy is discontinued at one month.

Boston Scientific is currently undertaking a well-powered study of DAPT discontinuation (EVOLVE Short DAPT) in EVOLVE II anatomically similar patients that are at high risk of bleeding. This study intends to supplement these data and is substantially different from EVOLVE SHORT DAPT in the following ways:

1. The study is intended to provide important evidence regarding the role of IVUS-guided stenting to facilitate the early cessation of DAPT.

2. SYNIVUS-DAPT examines DAPT cessation at 1 month as opposed to 3 months. To our knowledge, there are no other U.S. studies addressing this time course of DAPT discontinuation with any currently approved stents.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.2 RISKS ASSOCIATED WITH SYNERGY STENT® IMPLANTATION:

The SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent® System) is a device/drug combination product consisting of a drug/polymer-coated balloon expandable stent, pre-mounted on a Monorail (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr), which consists of platinum, chromium, iron, nickel, and molybdenum. It is indicated for improving luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries ≥2.25 mm to ≤4.0 mm in diameter in lesions ≤34 mm in length. The use of this product carries the risks associated with coronary artery stenting, including stent thrombosis, vascular complications, and/or bleeding events. Therefore this product should not be used in patients who are not likely to comply with recommended antiplatelet therapy.

Potential adverse events (in alphabetical order) which may be associated with the use of a coronary stent in native coronary arteries include but are not limited to:
Abrupt stent closure
Acute myocardial infarction
Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
Angina
Arrhythmias, including ventricular fibrillation and ventricular tachycardia
Arteriovenous fistula
Bleeding
Cardiac tamponade
Cardiogenic shock/pulmonary edema

Coronary aneurysm
Death
Dissection
Emboli, distal (air, tissue or thrombotic material or material from device(s) used in the procedure)
Heart failure
Hematoma
Hemorrhage, which may require transfusion
Hypotension/hypertension
Infection, local or systemic
Ischemia, myocardial
Pain, access site
Perforation or rupture of coronary artery
Pericardial effusion
Pseudo aneurysm, femoral
Renal insufficiency or failure
Respiratory failure
Restenosis of stented segment
Stent embolization or migration
Stent deformation, collapse, or fracture
Stent thrombosis/occlusion
Stroke/cerebrovascular accident/transient ischemic attack
Total occlusion of coronary artery
Vessel spasm
Vessel trauma requiring surgical repair or re-intervention

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

The amount of drug that circulates in the bloodstream following implantation of a SYNERGY™ Stentis several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day).

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

RISKS ASSOCIATED WITH DUAL ANTIPLATELET THERAPY

P2Y12 Inhibitors:

The main adverse event of this class of agents is bleeding.
The choice of P2Y12 inhibitor is at the investigator's discretion.

Clopidogrel (Plavix®)

For more information on clopidogrel please see clopidogrel or Plavix® package insert.

Prasugrel (Effient®)

Prasugrel can cause significant, sometimes fatal, bleeding.
Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke.
In patients who are ≥ 75 years of age, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered.
Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG).
When possible, discontinue prasugrel at least 7 days prior to any surgery.
Additional risk factors for bleeding include:

- Body weight < 60 kg
- Propensity to bleed
- Concomitant use of medications that increase the risk of bleeding

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of prasugrel.
If possible, manage bleeding without discontinuing prasugrel. Stopping prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.
For more information on pasugrel please see Effient® package insert.

Ticagrelor (Brilinta®)

Ticagrelor, like other anti-platelet agents, can cause significant, sometimes fatal bleeding.
Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage.
Do not start ticagrelor in patients undergoing urgent coronary artery bypass graft surgery (CABG).
If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events.

Maintenance doses of aspiring above 100 mg reduce the effectiveness of ticagrelor and should be avoided.
For more information on ticagrelor please see Brilinta® package insert.

RISKS ASSOCIATED WITH STUDY PARTICIPATION:
In addition to the aforementioned risks associated with the implantation of coronary stents, the use of everolimus, and 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.

2.3.3 KNOWN POTENTIAL 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 reduce cost, and reduce delays in non-cardiac procedures that require cessation of DAPT. This clinical trial has been designed to investigate potential benefits of the SYNERGY™ Stent with a shortened duration of dual antiplatelet therapy.

2.3.4 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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 healing profile of the SYNERGY™ Stent near-complete endothelialization of the stent occurs at 30 days), it is expected that treatment with 30 days 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.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine the safety of 1-month DAPT in a HBR patient population who are undergoing SYNERGY stent implantation.	Primary Endpoint: • Rate of cardiac death or myocardial infarction (SCAI definition) from 1 to 13 months post-index procedure in the "as	The specific endpoints are in accordance with EVOLVE Short DAPT (an approved FDA Trial). The 13 month endpoint

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	treated" (eligible for 30 day DAPT cessation) population. Secondary Endpoints • Rate of cardiac death or myocardial infarction (SCAI definition) from 1 to 13 months post-index procedure in the overall enrolled "intent-to-treat" patient population • Rate of Academic Research Consortium (ARC) definite/probable stent thrombosis (ST) involving the SYNERGY Stent's at 1 to 13 months post-index procedure • Rate of major bleeding (GUSTO severe/life threatening + moderate) at 1 to 13months post-index procedure • Ischemia-Driven (ID) Target Lesion Revascularization, • ID Target Vessel Revascularization, • Target Lesion Failure, • Target Vessel Failure, • All-Cause Death, and • All-Cause Death or MI.	is also in accordance with EVOLVE Short DAPT, in that the primary outcome is measured 12 months following DAPT cessation.

4 STUDY DESIGN

4.1 OVERALL DESIGN

SYNIVUS-DAPT is a prospective multicenter single-arm pilot study designed to characterize the safety of 1 month of dual antiplatelet therapy (DAPT) in a high bleeding risk (HBR) patient population who are undergoing iLab™ IVUS-guided percutaneous coronary intervention (PCI) with a SYNERGY™ Stent System.

Hypothesis – one (1) to thirteen (13) month rates of cardiac death or myocardial infarction (SCAI definition), and Stent thrombosis after Boston Scientific IVUS-guided SYNERGY™ Stents implantation will be low and provide key hypothesis-generating information to inform future larger scale clinical studies.

Patients will be screened as per standard of care (please see Section 1.3 Schedule of Activities). Eligible patients will undergo iLab™ IVUS-guided PCI with SYNERGY™ Stent System on Day 1 followed by safety laboratories (CBC w Diff, Platelets, Basic Metabolic Panel, PT/INR, CPK/CK-MB or troponin) and EKG within 24 hours of procedure completion. At 30 days (± 7 days) patient will return to clinic for evaluation, followed by phone follow up at 30 days post DAPT cessation (60 days post PCI) 6 months (± 14 Days) and at 12 months (± 30 days) post-DAPT cessation (7 and 13 months post-procedure) for evaluation of adverse events and endpoints.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed trial is designated as a prospective, single arm pilot investigation to assess safety endpoints following the application of DAPT in HRB patients undergoing iLab IVUS-guided PCI with the SYNERGY® Stent System.

The trial is designed as an observational, single arm, proof of concept study to determine if patients at high bleeding risk (HBR) who have IVUS guided SYNERGY™ Stent implantation can safely undergo DAPT cessation at 30 days post implantation. This is felt to be a prudent environment to appropriately and safely study this hypothesis and potentially enlighten future larger clinical trials.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:
General 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 >1 months of DAPT outweighs the benefit,
    - Need for 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,
- History of stroke (ischemic or hemorrhagic),
- Renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent),
- Platelet count ≥20,000/µL to ≤100,000/µL
- In the opinion of investigator, patient is at significant risk of falling
- Patient abuses drugs or alcohol
- Hemoglobin ≤ 11.0

2. Subject must be 18 years of age
3. Subject must be able to take study required dual antiplatelet therapy (1 month of P2Y12 inhibitor and aspirin, 13 months of antiplatelet monotherapy)
4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at the 1-month milestone if eligible per protocol
5. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific procedures are performed

Angiographic Inclusion Criteria

1. Subject must have had implantation of at least one SYNERGY™ Stent and the use of Boston Scientific IVUS for guided stent implantation
2. All implanted stents must be post dilated and must meet the following IVUS success criteria:
    a) Treated lesions in which the stent cross sectional area exceeds the distal reference cross sectional area
    b) The stent cross sectional area is less than the distal reference cross sectional area (if not additional post-dilatation must be performed, followed by repeat IVUS).
    c) Above IVUS success criteria must be met after the 2nd post dilatation

    Note: If IVUS success criteria is not met after the 2nd post dilatation then the patient is excluded
3. Stent procedure performed by an approved investigator
4. Vessel diameter ≥ 2.25 mm and ≤ 4.0 mm and lesion length ≤ 34mm
5. Pre-dilatation is up to the discretion of the investigator

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

General Exclusion criteria:

1. Subject with an indication for the index procedure of acute ST elevation MI (STEMI)
2. Subject with an indication for the index procedure of Non ST elevation MI (NSTEMI), based on the 3rd Universal MI definition
3. Subject with treatment with another coronary stent, other than SYNERGY, during the index procedure
4. Subject with a planned staged procedure > 7 days following the index procedure. (Note: Planned staged procedures are allowed if performed within 7 days of the index procedure and only when

SYNERGY™ stents are used for both the index and staged procedures). Discontinuation of DAPT should occur 1 month after the last PCI procedure is completed

5. A staged procedure cannot be in a 3rd epicardial vessel if 2 epicardial vessels were treated during the index procedure
6. Subject has a known allergy to:
    a. Contrast (that cannot be adequately pre-medicated),
    b. SYNERGY™ Stent system (e.g., everolimus. structurally related compounds, polymer or individual components) or
    c. Protocol-required concomitant medications (all P2Y12 inhibitors and aspirin)
7. Subject previously treated at any time with intravascular brachytherapy
8. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding
9. 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)
10. Subject intends to participate in an investigational drug or device clinical trial within 12 months following the index procedure (Note: registry, observational, data collection studies are not exclusionary)
11. Subject is judged inappropriate for discontinuation from P2Y12 inhibitor use at 1 month, due to another condition requiring chronic P2Y12 inhibitor use
    a. If at the 30 day visit the patient has had a peri-procedural NSTEMI with an enzyme elevation >5% of the upper 99th percentile of either CK-MB or Troponin, the subject should not be taken off DAPT.
12. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within (≤)1 month following index procedure
13. Subject is a woman who is pregnant or nursing
14. Subject with a current medical condition with a life expectancy of less than 12 months
15. Subject with implantation of a drug-eluting stent other than SYNERGY™ Stents within 11 months prior to index procedure
16. Have been previously consented for this trial and screen failed
17. Any other clinically significant comorbidities, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with interpretation of the study results, or predispose the patient to safety risks.

Angiographic Exclusion Criteria

1. Target lesion(s) is located within a saphenous vein graft or an arterial graft
2. TIMI flow 0 (total occlusion)
3. Target lesion(s) is located in the left main
4. Potential Target lesion(s) that involve a complex bifurcation (i.e. bifurcation lesion requiring treatment with more than one stent)
5. Thrombus, or possible thrombus, present in the target vessel (by visual estimate)
6. Patients requiring a treatment of more than two native epicardial vessels.
7. More than three lesions in two epicardial vessels unless they can be covered by one stent.
8. Target lesion(s) with in- stent restenosis

9. Treatment of non-target lesions or lesions not treated with a SYNERGY™ stent
10. Subject who did not receive Boston Scientific IVUS guided stent implantation and assessment
11. Any target lesion that has **not** been post dilated and has **not** received post dilatation IVUS
12. Patients who do not meet the following IVUS success criteria:
    - Target lesion(s) in which the stent cross sectional area is less than the distal reference cross sectional area and additional post-dilatation is not performed, followed by repeat IVUS.
      ** Note: If the IVUS success criteria is not met after the 2nd post dilatation the patient is excluded

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. Screen failure information will be reported to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. This will include demographic, screen failure details, eligibility criteria, and any serious adverse events (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Coordinators will be trained by the Coordinating Center at HonorHealth Research Institute. Participants will be screened for Eligibility, and Informed Consent will be obtained. Detailed procedural data will be obtained by the Study Coordinator and Site Principal Investigator, and participants will undergo a Baseline Interview. These data will be entered into the electronic data capture system with stringent protections and quality controls.
The SYNERGY™ Stent System is already FDA-approved for improving luminal diameter in patients with atherosclerotic lesions in native coronary arteries $\geq$ 2.25 mm to $\leq$ 4.0 mm in diameter in lesions $\leq$ 34 mm in length. This includes those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation MI or documented silent ischemia.

Pre Procedure Tests and Procedures (Up to 7 days prior to the procedure)

- Standard Laboratory Values: Basic Metabolic Panel, CBC w/ differential and platelets
- Cardiac Enzymes: Total CPK/CK-MB or Troponin I

- PT-INR: If not part of standard of care draw only if patient is taking warfarin, has liver disease or severe anemia
- 12 Lead ECG

Procedure

Study subjects will undergo PCI using the SYNERGY™ Stent System with iLab IVUS-guidance following the SYNERGY™IFU (instructions for use). If bailout stenting is required, a SYNERGY™ stent should be used if a stent of appropriate length and diameter is available. If not available, an approved coronary stent should be used.

Per the SYNERGY IFU:

- Target lesion vessel diameter ≥2.25mm and ≤ 4.0mm
- Target lesion length ≤ 34mm
- No ostial lesions (within 5 mm of RCA ostium, 3 mm of left main)
- No complex bifurcations
- No TIMI flow ≤ 1 distal to lesion
- No In-stent restenosis
- No CTOs
- No Overlapping stents

Per Protocol

- Pre dilatation per the investigators' discretion
- Post dilation is required for each implanted stent
- No more than 3 target lesions in 2 epicardial vessels
- Two target lesions in one epicardial vessel may be stented if at least 15mm apart or can be covered with one stent
- Post dilatation is required for all stents implanted followed by IVUS (for each stent). Up to 2 post dilations and IVUS can be done for each implanted stent
- If two target lesions are treated, post-procedure IVUS imaging must be done on the first target lesion after its successful treatment, and then after successful treatment of the 2nd target lesion

IVUS Guide (see Amendment 1)

- All target lesions must have IVUS post dilatation followed by IVUS
- If the stent is not fully opposed the stent must be re-dilated and IVUS repeated after each dilatation
- If the cross sectional area of the stent is less than the distal vessel diameter after the 2nd post dilatation and repeat IVUS, the patient is excluded

Bailout Stenting

IF a bailout stent is required it is recommended to use a SYNERGY™ Stent. IVUS must be done per the IVUS protocol for any bailout stents used.

Post Procedure (Prior to Discharge)

- Post procedure labs: BMP, CBC with diff and platelets, cardiac enzymes (CPK, CK–MB or Troponin I) 2 sets 6-8 hours apart
- Note: if patient is being discharged the same day draw one set of cardiac enzymes immediately post procedure and one set at 6 hours post procedure.
- 12 Lead ECG

Post PCI Follow up Visits

Follow up visits will occur at 30 and 60 days post PCI, and 7 and 13 months post PCI

1. 30 Day Post PCI Visit (+ 7 days) in person Visit:
   Requirements:
   - Angina Assessment including completion of the angina assessment questionnaire
     - Evaluate for cardiac events: recurring angina, unstable angina, revascularization (TLR or other) or another condition in the opinion of the investigator would prevent stopping DAPT
   - Assessment of adherence to DAPT: Interruptions, missed doses, changes in DAPT Medication
   - Adverse event assessment and reporting
   - Cardiac con medications (including Aspirin)
   - DAPT cessation

2. 60 Day, 7 Month and 13 Month Post PCI Visits
   - Angina Assessment
   - Assessment of adherence to Aspirin: Interruptions, missed doses, changes in DAPT Medication
   - Adverse Event assessment including evaluation for cardiac events: Recurring angina, unstable angina, revascularization (TLR or other) or other conditions
   - Cardiac con medications (including Aspirin and any reintroduction of P2Y12)

6.1.2 DOSING AND ADMINISTRATION

Antiplatelet Medications

DAPT Regimen (aspirin + P2Y12 inhibitor) will be reported in the electronic case report form (eCRF) to include the period of time 72 hours prior to the index procedure through the end of the study. Pertinent information regarding the use of antiplatelet medications including dose changes, medication interruptions (greater than 3 days), and medication cessation, must be documented. Post-PCI dosing should be administered in accordance with the individual agents' directions for use (e.g., consistent with warning, precautions, and dose adjustments if needed)

At the discretion of the Investigator patients on warfarin or NOAC may be discharged on the anticoagulant and a P2Y12 without Aspirin. Additionally at the time of the 30 day visit, if the patient continues on the anticoagulant, the P2Y12 may be stopped and low dose Aspirin (81 mg) may be started.

P2Y12 Inhibitor Loading and Discharge Dosing

- For subjects who have been taking a P2Y12 inhibitor for ≥ 72 hours prior to the time of the index procedure, a loading dose will not be required.

- For subjects who have not been taking a P2Y12 inhibitor for ≤ 72 hours at the time of the index procedure, a loading dose will be recommended to be administered prior to the index procedure or not more than 2 hours after the index procedure. The following doses are recommended:

  Clopidogrel: A peri-procedural loading dose of 600 mg PO x 1 or 75 mg PO daily for 4 days is recommended. A post-procedural daily dose of 75mg will be recommended.

  Prasugrel: A peri-procedural loading dose of 60 mg is recommended. A post procedural daily dose of 10 mg will be recommended.

  Ticagrelor: A peri-procedural loading dose of 180 mg is recommended. A post procedural dose of 90mg BID will be recommended

Aspirin Loading Dose

- For subjects who have been taking Aspirin daily (regardless of the dose) for ≥ 72 hours prior to the time of the index procedure, a loading dose will not be 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 (325mg) is recommended prior to the index procedure. The dosage of the loading dose is at the discretion of the Investigator with a recommendation that it is administered prior to the index procedure.
- A post procedural dose of Aspirin 81mg is recommended.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study participants will undergo SYNERGY™ Stent implantation and receive prescriptions for aspirin and the investigator's choice of P2Y12 inhibitor. Antiplatelet agents and SYNERGY™ Stent are commercially available and will not be provided as part of this study.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable. This is not a randomized study.

6.4 STUDY INTERVENTION COMPLIANCE

Compliance to DAPT regimen will be ascertained at the 1-month follow-up visit and will be used to determine if the subject is eligible for discontinuation of P2Y12 inhibitor. During the 1-month follow-up visit, the subject will also be asked about any significant interruptions (greater than 3 days) in the prescribed index procedure.

Follow up at 30 days post DAPT cessation either by phone or clinic visit to assess angina status and targeted endpoints.

Note: All enrolled subjects who receive a SYNERGY™ Stents must be followed at all milestones through 13-months, regardless of eligibility to discontinue DAPT.

6.4.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY PARTICIPATION

Subjects should not discontinue P2Y12 inhibitor (the patient will remain in the study until 13 months unless consent to participate is withdrawn) at 1 month if any of the following criteria are met:

- Subject experiences a stroke, MI, PCI, CABG and/or stent thrombosis, during the 1 month period following the index procedure
- Subject is non-compliant with DAPT regimen during the 1 month period following the index procedure. Non-compliant is defined as: DAPT interruption for at least 3 days.
- Subject judged to have another condition rendering them inappropriate for discontinuation from P2Y12 inhibitor at 1 month.

An investigator may discontinue or withdraw a participant from the study if:

- Pregnancy occurs
- Significant study non-compliance beyond DAPT compliance issues

- Continued participation in the study would not be in the best interest of the participant due to other conditions
- The participant is unwilling or unable to discontinue DAPT within 7 days after 30-day post-procedure visit
- Other unforeseen reason

Additionally, participants may withdraw from participation in the study at any time upon their own discretion and a request to the site.

The reason for participant discontinuation or withdrawal from the study will be recorded on Case Report Form (CRF). Subjects who sign the informed consent form but screen fail due to inclusion or exclusion criteria requirements will be replaced.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for any of the study follow-up visits and/or is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).
All serious adverse events (SAE), adverse device effects (ADE), death, MI, stent thrombosis, as well as bleeding events will be collected from the start of the index procedure (sheath insertion) through the 13-month follow-up visit.

Specific Definitions of Adverse Events:

DEATH
All deaths are considered cardiac unless a non-cardiac cause can be documented.

- 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.
- Non-cardiac death: Any death not covered by the above definition, including death due to pulmonary causes, accident, suicide, infection, sepsis, or trauma.

STENT THROMBOSIS

We intend to use the ARC Definite/Probable definition of stent thrombosis

Definite Stent Thrombosis:

- Angiographic or pathologic confirmation of intracoronary stent thrombosis either inside or 5mm proximal or distal to the stent.

AND

- Symptoms suggestive of an acute coronary syndrome:
  - 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)

Probable Stent Thrombosis:

- unexplained death within 30 days
- target vessel myocardial infarction without angiographic confirmation of stent thrombosis

GUSTO Severe/life-threatening or moderate bleeding

- 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

MYOCARDIAL INFARCTION –SCAI Definition – Procedural Related MI

Group	**Definition**

Normal baseline CK-MB	CK-MB rise of ≥10x ULN or >5x ULN with new pathologic Q-waves in at least 2 contiguous leads or new persistent left bundle branch block OR In the absence of baseline CK-MB, a cTn rise of ≥70x ULN or a rise of ≥35 ULN plus new pathologic Q-waves in at least 2 contiguous leads or new persistent left bundle branch block
Elevated baseline biomarkers that are stable or falling	A CK-MB or cTn rise that is equal (by an absolute increment) to the definitions described for patients with normal CK-MB at baseline.
Elevated baseline biomarkers that have not been shown to be stable or falling	A CK-MB or cTn rise that is equal (by an absolute increment) to the definitions described for patients with normal CK-MB at baseline *Plus* New ST-segment elevation or depression *Plus* New-onset or worsening heart failure or sustained hypotension or other signs of a clinically relevant MI.

Spontaneous MI:

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

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death, a life-threatening adverse event,

- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 CLASSIFICATION OF AN ADVERSE EVENT

8.1.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.1.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.1.3.3 EXPECTEDNESS

The principal investigator in consultation with the sponsor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.1.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.1.5 ADVERSE EVENT REPORTING

Any adverse experience that occurs in this study that is serious, unexpected, and related or probably related to the study design must be reported to the IRB of record within 10 working days after the investigator first receives a report of the event by completing and submitting an adverse event report form as per IRB of record policy and procedures.

Any unanticipated adverse device effects must be reported to the IRB within 10 working days after the investigator first learns of the event by completing and submitting an adverse event report for as per IRB of record policy and procedures.

All adverse events that do not meet the above reporting requirements should be summarized and provided to the IRB at the time of continuing review.

8.1.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator will immediately, but no longer than within 5 working days after investigator first becomes aware of the event, report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event. In that case, the investigator must immediately report the event to the sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.1.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.1.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.1.9 REPORTING OF PREGNANCY

If a female patient becomes pregnant while participating in this study and receiving DAPT, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6-8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be recorded as an AE or SAE.

8.2 UNANTICIPATED PROBLEMS

8.2.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, 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 (21 CFR 812.3(s)).

8.2.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 5 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within10 working days of the investigator becoming aware of the problem.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b) (1)).

8.2.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems that are determined to be related or probably related to the study intervention will be shared with the patients at the following visit after informed consent approved by IRB of record.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Outcome measures include 1-13 month post-procedure rates of cardiac death and myocardial infarction. This single-arm prospective design will compare rates on the dependent variables following

Boston Scientific IVUS-guided SYNERGY™ Stent implantations with standard of care rates in the target population. The null and alternative hypotheses are as follows:

$H_0 = p = p_0$

The null hypothesis states that there is no difference on myocardial infarction or cardiac death rates.

$H_1 : p < p0$

9.2 THE ALTERNATIVE HYPOTHESIS STATES THAT PATIENTS UNDERGOING SYNIVUS-DAPT TREATMENT WILL HAVE LOWER RATES OF MYOCARDIAL INFARCTION OR CARDIAC DEATH. SAMPLE SIZE DETERMINATION

An a priori power analysis was conducted for a one-sample binomial test with an alpha of .05 (one-tailed), beta of .05, constant proportion (*p*) of .031, and assumed primary endpoint proportion of 0.0047 resulting in a needed sample size of 231.
The consideration of historical data on timing and incidence of myocardial infarction and stent thrombosis from published meta-analysis and related literature, the SCAAR registry and ACS subsets (De Luca, Dirksen, Spaulding, et al, 2012; Ellis, Colombo, Grube, et al, 2007; Palmerini, Biondi-Zoccai, Riva, et al, 2012; Palmerini, Kirtane, Serruys, et al, 2012; SCAAR registry and ACS subset, 2016). Historic rates at 1-year follow up for ST showed variability ranging from 0.3 to 5.3%. Rates of MI range from 1.9 to 8.8%. A time-to-event bivariate exponential distribution function was used to determine criteria for sample sizes based on a 95% power determination resulting in a historic rate determination of 3.1%. Patients lost to follow-up will not be included in the final analysis, and additional patients will be recruited for study participation to reach the needed sample of 231.

The FDA has approved an initial phase of the investigation for 100 U.S patients. Accordingly, the sample size of N=100 for the initial phase is not statically based. Should approvals for study continuation be granted, the total sample size for subsequent phases will remain at 231, inclusive of subjects enrolled on this initial phase.

9.3 POPULATIONS FOR ANALYSES

The Intention-to-Treat (ITT) Analysis Dataset inclusive of all participants will be included in the analysis. This is inclusive of all safety endpoints and encompasses the safety analysis dataset. Patients lost to follow-up will not be included in planned analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All patients will be enrolled in the study with hospital IRB approval after consent. Preliminary data collected will include clinical history and demographic data. Descriptive statistics on patients' demographic characteristics and echocardiographic parameters will be reported as means and standard deviations for continuous variables and frequency counts for categorical variables.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

For primary endpoints:

Prevalence rates of cardiac death and myocardial infarction will be determined for the sample. The binomial test will be conducted to test the significance of deviations from the expected distribution of observations dichotomized as "*did not occur*" or as "*occurrence*" for each outcome.

For *safety endpoints*:

Prevalence rates for safety outcomes including ischemia-driven (ID) target lesion revascularization, ID target vessel revascularization, target lesion failure, target vessel failure, all-cause death, and myocardial infarction will be evaluated with binomial tests.

The test formula to be used is as follows:

$P(X) = C^{n}_{k}\ p^{k}(1-p)^{n-k}$

All data will be screened for non-parametric statistical test assumptions. Accordingly, all dichotomous outcomes will be screened for exclusivity and appropriateness for inclusion in data analysis. Missing data, nonadherence and data lost to follow-up will be excluded from the final analysis.

The a priori alpha level for all statistical tests will be set at .05. To adjust for a potentially inflated family-wise error rate, the Bonferroni correction (α/m) will be applied for multiple tests with the same sample.

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics on patients' demographic characteristics and echocardiographic parameters will be reported as means and standard deviations for continuous variables and frequency counts for categorical variables. Rate to occurrence or prevalence data will be analyzed for this proposed study, and as such, repeated measures analysis from baseline are not applicable.

9.4.4 PLANNED INTERIM ANALYSES

A 7 month planned interim analysis for the first 50 patients enrolled using the O'Brien-Fleming method will be conducted for cardiac death or myocardial infarction rate. Using an a priori alpha of .05, the adjusted alpha for the interim analysis will be 0.0054 and 0.0492 for the final analysis for consideration of frequency rates and obtained p-values at each analysis time point. Interim analysis outcomes will be used to assess trial efficacy, early evidence of harm, and safety to inform futility determinations and continuation considerations. Frequency rates on each outcome variable that exceed the non-inferiority margin of ±5% for the interim analysis will result in temporary halting for further safety evaluations. The project statistician will conduct the planned interim analysis results will be reviewed by the study PI and research team.

9.4.5 SUB-GROUP ANALYSES

The *F* test of stability (or Chow test) for the coefficients of a panel model will be used to examine outcomes according to site and region and to test for the presence of individual effects.

$$F1\text{−way} = \frac{(ESS_R - ESS_U) / (N - 1)}{ESS_U / ((T - 1)\, N - K)}$$

ESS_R denotes the residual sum of squares under the null hypothesis and ESS_U the residual sum of squares under the alternative. Under H_0, the statistic F1−way is distributed as F with (N − 1, (T − 1)N − K) degrees of freedom. Accordingly, the null hypothesis is as follows:

$H_0 : \mu i = 0, i = 1, \ldots, N.$

Additional subgroup analyses will be conducted to examine potential differences in women and ethnic/racial minorities.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by each study outcome following the procedure to study cessation at 13 months. Any occurrence of cardiac death, myocardial infarction, and stent thrombosis prior to this time will be documented accordingly.

9.4.7 EXPLORATORY ANALYSES

No additional exploratory or auxiliary analyses are planned for the investigation.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Informed Consent Form
- Angina Questionnaire

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, funding agency, Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional

Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at HonorHealth Research Institute. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by HonorHealth Research Institute research staff will be secured and

password protected. At the end of the study, all study databases will be de-identified and archived at the HonorHealth Research Institute.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at HonorHealth Research Institute.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
David G. Rizik, MD	Bimal Padaliya, MD
HonorHealth	HonorHealth
10510 N. 92nd Street Suite 300, Scottsdale, AZ 85258	10200 N. 92nd Street Suite 150 Scottsdale, AZ 85258
480-882-7450	490-882-7450
DavidRizik@aol.com David.Rizik@HonorHealth.com	bimalpadaliya@gmail.com Bimal.Padaliya@HonorHealth.com

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise in cardiology, pharmacology and biostatistics. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least quarterly to assess safety and efficacy data of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial will be in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), Food & Drug Administration (FDA) and with applicable regulatory requirement(s). HonorHealth will be responsible for monitoring of this study. One hundred percent of source documentation related to safety (AE-SAE) will be monitored. Twenty-five percent of all other source documentation will be monitored. Refer to the Clinical Monitoring Plan.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), Food & Drug Administration (FDA) and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered in electronic case report forms (eCRF), a 21 CFR Part 11-compliant data capture system provided by HonorHealth Research Institute. The data system includes password protection and internal quality checks, such as automatic range checks, to identify

data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, Food and Drug Administration (FDA), International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to HonorHealth Research Institute. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-

reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting David G Rizik, MD

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical or device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with HonorHealth has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NOAC	Novel Oral Anticoagulant
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class

SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 DATA SAFETY MONITORING COMMITTEE

An independent data safety and monitoring committee (DSMC) will be formed to evaluate the safety and effectiveness of the study intervention for each subject as well as study conduct of each site. The DSMC will also review all SAEs reported by each site. The DSMC will review study data to determine if endpoints are being met and if the study can continue with or without changes to the protocol or if the study should be terminated immediately due to safety concerns or lack of data to support study endpoints. Findings and recommendations of the DSMC will be reported to the sponsor after each meeting. The DSMC will also serve as the clinical events committee (CEC). The DSMC will meet on a quarterly basis or more frequently as needed if safety concerns are raised. Data reported to HonorHealth will be received by the lead principal investigator on a regular basis and not less than once a month. In addition, SAEs will be reported to HonorHealth immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the lead principal investigator, the medical monitor, and the site principal investigators who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. A planned interim analysis will be performed (Section 9.4.4).

10.4 IVUS ACQUISITION PROTOCOL

Use of IVUS prior to stent implantation is not mandatory but encouraged.

Post-stent-implantation IVUS examination with a Boston Scientific Opticross IVUS catheter and the POLARIS software system is mandatory for each implanted stent.

Post-PCI IVUS criteria for stent optimization requires that the minimal stent cross-sectional area is greater than the lumen cross-sectional area at a distal reference segment.

IVUS with any catheter frequency can be used but must be with a Boston Scientific catheter and on the Polaris system

* After the final post stent dilatation:

1) Place the IVUS catheter imaging sensor at least 10mm distal to the target lesion

2) Perform an IVUS run by pulling back to at least 10mm proximal to the target lesion.

3) Measure cross sectional area of the least diseased frame within 10mm distal to the stent (distal reference)

4) Measure cross sectional area of the frame with the smallest diameter within the stent

5) If the cross sectional area of the frame within the stent is greater than cross sectional area of the distal target, then the IVUS success criteria has been met

6) If the cross sectional area of the frame within the stent is less than the cross sectional area of the distal target, then perform high pressure post dilatation of the stent and then repeat steps 1 through 6

Note: If the stent cross sectional area is less than the target lesion distal reference diameter after the 2nd post dilatation and IVUS the patient is excluded.

If two target lesions are treated, post-procedure imaging must be done on the first target lesion after its successful treatment, and then after successful treatment of the 2nd target lesion.

* Administer 100-200 µg of intracoronary nitroglycerine before all IVUS examinations.

Caution: It is important to place the IVUS catheter at the center of the vessel lumen to avoid disturbing the device struts.

PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	9May2018	Sections 1.1 Endpoints and 3.0 Objectives and Endpoints have been clarified Section 1.1 - Clarified multi-center study to reflect 2 other sites Section 1.3 – clarified Scheduled of Events to include cardiac troponin follow-up in case of elevated levels Section 4.1 – removal of post-procedure consenting and harmonize 12 months post-DAPT = 13 months post-procedure Section 1.1 and 5.1 added inclusion criteria for a maximum of 2 native epicardial vessels/maximum 2 lesions/vessel. Section 5.2 – changes saphenous vein graft to index procedure SVG PCI Section 5.2 – clarified exclusion criteria #4, #7, #24, #25 Section 6.1.2 – included tracking of all anti-platelets interruptions greater than 1 day and post-index procedure recommendations on anti-platelet drugs dosages Section 7.1 – clarified language for replacement of consented/enrolled patients Section 8.1.1 – addition of definitions Section 9.1 – updated Statistical Considerations Section 9.4.2 and 10.1.8 – updated to include plan for handling missing data Section 10.1.7 – clarified monitoring plan Added IVUS Acquisition Protocol – Appendix A.	Corrections requested by CDRH (FDA)
3.0	14Jul2018	Section 7.1 – removed criteria for subject discontinuation	Corrections requested by CDRH (FDA)
4.0	1Oct2018	Added NCT number Section 1.1 Synopsis under Study Population Inclusion Criteria and Section 5.1 Inclusion Criteria 2nd bullet: Need for chronic or lifelong anticoagulation therapy. An explanation for Atrial fibrillation patients has been added to clarify that these patients are eligible. Section 1.1 Synopsis under Study Population Exclusion Criteria and Section 5.2 Exclusion Criteria item #4: Clarification on the exclusion for patients undergoing peri-	Clarifications requested by the DSMC/CEC

		procedural NSTEMI that states in patients with an enzyme elevation => 5% of the upper 99th percentile are excluded Sections 1.1 and 5.2 - Exclusion Criteria; added item #26 - Any other clinically significant co-morbidities, which in the judgement of the Investigator could compromise compliance, interfere with study results or predispose patient to safety risks. Section 1.3 Schedule of Events: Deleted CPK/CK-MB and replaced with Troponin. This is to reflect the standard monitoring.	
4.1	09Sept2019		

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