PROTOCOL 10-392

ABSORB III
RANDOMIZED CONTROLLED TRIAL

A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects with *de novo* Native Coronary Artery Lesions

Version Number	Version 17.0
Date	August 16, 2018
Principal Investigators and Study Chairman	**Principal Investigators:** Stephen G. Ellis, MD, Cleveland Clinic, Cleveland OH Dean J. Kereiakes, MD, The Christ Hospital, Cincinnati, OH **Study chairman:** Gregg W. Stone, MD, Columbia University Medical Center, New York, NY
Planned Number of Sites and Region(s)	A maximum of 220 sites in the United States and outside the United States
Abbott Vascular Medical Expert	Krishna Sudhir, Divisional Vice President Medical Affairs, Chief Medical Office
Trial Type	Prospective, randomized, single-blind, multi-center trial
Sponsor / Data Monitoring/ Data Management/Data Analysis	Abbott Cardiovascular Systems, Inc. 3200 Lakeside Drive Santa Clara, CA 95054
Trial Monitor	Abbott Vascular
Enrollment/Randomization Service	Bracket 303 2nd Street, Suite 700 South San Francisco, CA 94107
Electronic Data Capture Software	Medidata RAVE
Angiographic Core Laboratory	Beth Israel Deaconess Medical Center, Angiographic Core Laboratories, Boston, MA
Intravascular Ultrasound (IVUS) Core Laboratory	Cardiovascular Core Analysis Laboratory (CCAL), Stanford, CA
Optical Coherence Tomography (OCT) Laboratory	University Hospitals Cardiovascular Imaging Core Laboratory, Cleveland, OH
Clinical Events Committee	Cardiovascular Research Foundation, New York, NY
Data Safety Monitoring Board	Axio Research, Seattle, WA
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TABLE OF CONTENTS

COMPLIANCE STATEMENT:

This trial will be conducted in accordance with this Protocol/Clinical Investigational Plan, the declaration of Helsinki, applicable good clinical practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812, OUS ISO14155) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB)/ Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.)

Sponsor Signatory Representative:

Approval for this protocol and any subsequent amendments shall be obtained per Abbott Vascular Standard / Detailed Operating Procedure(s).

PROTOCOL SUMMARY

Trial Name and Number	**ABSORB III Randomized Controlled Trial: 10-392**
Title	**THE ABSORB III RANDOMIZED CONTROLLED TRIAL (RCT)**
Investigational Device	Absorb™ Bioresorbable Vascular Scaffold (BVS) System[1]: • Scaffold diameters: 2.5, 3.0 and 3.5 mm • Scaffold lengths[2]: 8, 12, 18, and 28 mm The 3.0 x 18 mm Absorb BVS will be used for the Lead-In.
Control Device	Commercially approved XIENCE Family Stent System, inclusive of XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro (OUS only),and XIENCE Pro^X (OUS only)[3] • Stent diameters: 2.5, 2.75, 3.0, 3.25*, 3.5 and 4.0 mm • Stent lengths: 8, 12, 15, 18, 23, and 28 mm XIENCE Family Stent System will hereinafter be called "XIENCE" in this study. *The 3.25 mm is only available for XIENCE Xpedition

Objectives	• **ABSORB III Primary Objective:** The pivotal trial to support the US pre-market approval (PMA) of Absorb BVS. ABSORB III will evaluate the safety and effectiveness of the Absorb BVS System compared to the XIENCE in the treatment of subjects, including those with diabetes mellitus, with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels.
	• **ABSORB III Secondary Objectives:**
	  • **Lead-In Phase Objective:** To evaluate the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice.
	  • **Imaging Cohort Objective:** To evaluate long-term vascular function and patency of the Absorb BVS treated segments compared to XIENCE treated segments in the treatment of subjects with ischemic heart disease caused by up to two de

[1] The commercially approved CE marked device will be used in geographies where it is commercially available.
[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 mm diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.
[3] For geographies where these devices are commercially available, the investigational sites may use only their locally approved devices.

	novo native coronary artery lesions in separate epicardial vessels.
Study Design	A prospective, randomized (2:1 Absorb BVS to XIENCE), single-blind, multi-center trial, registering approximately 2250 subjects. • The primary endpoint data from this trial will support US premarket approval (PMA) of Absorb BVS and label claims of non-inferiority of Absorb BVS as compared to XIENCE in 1-year target lesion failure (TLF). The ABSORB III trial also includes a Lead-In Phase and an Imaging Cohort: • **Lead-In Phase:** A non-randomized, single-arm, open label group of up to 50 subjects treated with Absorb BVS at up to 35 US sites. The Lead-In phase will enroll/register subjects prior to the randomization phase of ABSORB III. • **Imaging Cohort:** A prospective, randomized (2:1 Absorb BVS to XIENCE), single-blind, multi-center trial, registering approximately 200 subjects. This includes 150 subjects for the angiographic/IVUS endpoints analysis and approximately 50 subjects for OCT endpoints analysis. The 200 subjects are separate from the 2000 subjects included in the primary analysis. The powered secondary endpoint data from this cohort will support label claims of superiority of Absorb BVS as compared to XIENCE specific to vasomotion and late lumen enlargement The Lead-In Group and Imaging Cohort will operate under the ABSORB III trial. The Lead-In Group will enroll/register first. After the completion of Lead-In, the rest of ABSORB III subjects (including Imaging Cohort) will start to enroll/register. All trial elements will apply to ABSORB III, including the Lead-In Group and the Imaging Cohort, unless otherwise specified.
ABSORB III Primary Endpoint	**ABSORB III Primary Endpoint** 1. TLF at 1 year, non-inferiority (NI) against the control. • TLF is defined as composite of Cardiac Death, Myocardial Infarction attributable to Target Vessel (TV-MI), or Ischemia-Driven Target Lesion Revascularization (ID-TLR). • This analysis will include ~2000 subjects.

Powered Imaging Cohort Secondary Endpoints	Imaging secondary endpoints are based on the pooled subjects from the Imaging Cohort of ABSORB III (~ 200 angiographic subjects and ~150 IVUS subjects) and subjects from the ABSORB Japan RCT (~ 400 angiographic subjects, and ~150 IVUS subjects). 1. The in-stent/scaffold mean lumen area change, from post-procedure to 3 years by IVUS (mean lumen area measured after nitrate infusions, superiority test, ~300 pooled subjects). 2. The in-stent/scaffold mean lumen diameter change, between pre- and post-nitrate infusion at 3 years by angiography (superiority test, ~600 pooled subjects).
Powered Secondary Endpoint for Angina	Angina at 1 year test for superiority of Absorb BVS to XIENCE. • Angina is defined as the first adverse event resulting in the site diagnosis of angina. • The analysis will exclude angina following the index procedure through discharge, not to exceed a period of 7 days This analysis will include ~2000 subjects.
Powered Secondary Endpoint for All Revascularization	All revascularization at 1 year test for superiority of Absorb BVS to XIENCE. This analysis will include ~2000 subjects.
Powered Secondary Endpoint for Ischemia-Driven Target Vessel Revascularization	Ischemia-driven target vessel revascularization at 1 year testing for superiority of Absorb BVS to XIENCE This analysis will include ~ 2000 subjects.
Powered Secondary Endpoint for Diabetic Indication	The powered secondary endpoint will be used to support a diabetic indication for Absorb BVS.
Patient Reported Outcome (PRO) Informational Endpoints	Patient-reported outcomes are informational endpoints to assess Health-Related Quality of Life at baseline, 30 days, 1, 2, 3 and 5 years follow-up. The following questionnaires will be used in this study: • EuroQoL 5D (EQ-5D) survey to assess overall health status • Seattle Angina Questionnaire (SAQ) to assess disease-specific Quality of Life • Rose Dyspnea Scale (RDS) to assess severity of dyspnea. • Generalized Anxiety Disorder scale (GAD-7) to assess anxiety. Notes:

	PRO endpoints will be evaluated in the 2,000 primary analysis subjects of ABSORB III and not the lead-in or imaging subjects. At 5 years, only EQ-5D and SAQ will be administered.
Subject Enrollment, Randomization and Registration	• Subjects are considered enrolled in ABSORB III after signing the Informed Consent. • Subjects are considered randomized in ABSORB III after the interactive voice response system (IVRS) has been called and a device (Absorb BVS or XIENCE) has been assigned. • Subjects are considered registered in the ABSORB III upon randomization. • Enrolled subjects not randomized in the trial will be considered screen failures and will not be followed. • Lead-In subjects will be considered registered upon calling IVRS. Refer to Figure 1 in Appendix IV.
Clinical Follow-Up	All subjects in the ABSORB III (including the Lead-In and Imaging Cohort) will receive the following clinical follow-up: o 30 ± 7 days follow-up telephone contact/office visit o 180 ± 28 days follow-up telephone contact/office visit o 1 year ± 28 days office visit and electrocardiogram (ECG) o Annual visits: 2-5 years ± 28 days follow-up telephone contact/ office visit
Imaging Follow-Up for the Imaging Cohort	A select number of sites with intravascular ultrasound (IVUS) only or IVUS and optical coherence tomography (OCT) capabilities will be selected to enroll the 200 subject Imaging Cohort. These subjects will have additional evaluations: o Post-procedure: angiography and IVUS (~150 subjects) or angiography and OCT (~50 subjects) o 3 years ± 28 days: angiography, IVUS and ECG for approximately 150 subjects, OR o 3 years ± 28 days: angiography, OCT and ECG for approximately 50 subjects All subjects in Imaging Cohort must have received the assigned device. Imaging Cohort subjects are required to undergo imaging at 3 years.
Patient Reported Outcome (PRO) Follow-Up	All 2,000 subjects in the primary analysis will receive the following PRO follow-up assessments:

	○ 30 ± 7 days follow-up telephone contact/office visit (EQ-5D, SAQ, RDS, GAD-7) ○ 1, 2 and 3 year ± 28 days office visit (EQ-5D, SAQ, RDS, GAD-7) ○ 5 year ± 28 days follow-up telephone contact/ office visit (EQ-5D, SAQ)
ABSORB III Primary Analysis Sample Size Justification	ABSORB III Primary Analysis: Sample size of this study is based on primary endpoint of 1 year TLF using the following assumptions: • True rate of 1-year TLF is 7.0% for both Absorb BVS and XIENCE • One-sided alpha = 0.025 • Non-inferiority margin = 4.5% • Power = 96% Sample size of 1900 subjects is required for the study (2:1 randomization); 1267 subjects for Absorb BVS arm and 633 subjects for XIENCE arm. Assuming a 5% dropout rate approximately 2,000 subjects will be required.
Imaging Cohort Analysis Sample Size Justification	Imaging Cohort Secondary Endpoint Analysis: The assumptions of sample size of this study are detailed in Section 10.3.2.
Inclusion Criteria	**General Inclusion Criteria** 1. Subject must be at least 18 years of age. 2. Subject or a legally authorized representative must provide written Informed Consent prior to any study related procedure, per site requirements. 3. Subject must have evidence of myocardial ischemia (e.g., stable, unstable angina, post-infarct angina or silent ischemia) suitable for elective PCI. Subjects with stable angina or silent ischemia and < 70% diameter stenosis must have objectives sign of ischemia as determined by one of the following, echocardiogram, nuclear scan, ambulatory ECG or stress ECG). In the absence of noninvasive ischemia, fractional flow reserve (FFR) must be done and indicative of ischemia. 4. Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery. 5. Female subject of childbearing potential who does not plan pregnancy for up to 1 year following the index procedure. For a female subject of childbearing potential a pregnancy test must

	be performed with negative results known within 7 days prior to the index procedure per site standard. 6. Female subject is not breast-feeding at the time of the screening visit and will not be breast-feeding for up to 1 year following the index procedure. 7. Subject agrees to not participate in any other investigational or invasive clinical study for a period of 1 year following the index procedure.[4] **Angiographic Inclusion Criteria** 1. One or two *de novo* target lesions: a. If there is one target lesion, a second non-target lesion may be treated but the non-target lesion must be present in a different epicardial vessel, and must be treated first with a successful, uncomplicated result prior to randomization of the target lesion. b. If two target lesions are present, they must be present in different epicardial vessels and both must satisfy the angiographic eligibility criteria. c. The definition of epicardial vessels means the LAD, LCX and RCA and their branches. Thus, the patient must not have lesions requiring treatment in e.g. both the LAD and a diagonal branch. 2. Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥ 50% and < 100% with a TIMI flow of ≥ 1 and one of the following: stenosis ≥ 70%, an abnormal functional test (e.g., fractional flow reserve, stress test), unstable angina or post-infarct angina. a. Lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.50 mm and ≤ 3.75 mm. b. Lesion(s) must be located in a native coronary artery with length by visual estimation of ≤ 24 mm. c. For Lead-In subjects with 3.0x18 mm Absorb BVS: lesions (s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.75 mm and ≤ 3.25 mm. The lesion length by visual estimation is ≥ 8 mm and ≤ 14 mm.
Exclusion Criteria	**General Exclusion Criteria**

[4] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

	1. Any surgery requiring general anesthesia or discontinuation of aspirin and/or an ADP antagonist is planned within 12 months after the procedure. 2. Subject has known hypersensitivity or contraindication to device material and its degradants (everolimus, poly (L-lactide), poly (DL-lactide), lactide, lactic acid) and cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated. 3. Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to clopidogrel and prasugrel and ticagrelor; or to heparin and bivalirudin, and therefore cannot be adequately treated with study medications. 4. Subject had an acute myocardial infarction (AMI; STEMI or NSTEMI) within 72 hours of the index procedure and both CK and CK-MB have not returned to within normal limits at the time of index procedure; or subject with stable angina or silent ischemia has CK-MB that is greater than normal limits at the time of the index procedure. 5. Subject is currently experiencing clinical symptoms consistent with new onset AMI (STEMI or NSTEMI), such as nitrate-unresponsive prolonged chest pain with ischemic ECG changes. 6. Subject has a cardiac arrhythmia as identified at the time of screening for which at least one of the following criteria is met:[5] a. Subject requires coumadin or any other agent for chronic oral anticoagulation. b. Subject is likely to become hemodynamically unstable due to their arrhythmia. c. Subject has poor survival prognosis due to their arrhythmia. 7. Subject has a left ventricular ejection fraction (LVEF) < 30% assessed by any quantitative method, including but not limited to echocardiography, MRI, Multiple-Gated Acquisition (MUGA) scan, contrast left ventriculography, PET scan, etc. LVEF may be obtained within 6 months prior to the procedure for subjects with stable CAD. For subjects presenting with ACS, LVEF must be assessed during the index hospitalization (which may include during the index procedure by contrast left ventriculography) but prior to randomization in order to confirm the subject's eligibility. 8. Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if performed anytime >30

[5] Investigator should use discretion when enrolling subjects with high CHADS scores.

	days before the index procedure, or between 24 hours and 30 days before the index procedure if successful and uncomplicated. 9. Subject requires future staged PCI either in target or non-target vessels or subject requires future peripheral interventions < 30 days after the index procedure 10. Subject has received any solid organ transplants or is on a waiting list for any solid organ transplants. 11. At the time of screening, the subject has a malignancy that is not in remission. 12. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy. 13. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum. 14. Subject is receiving or will require chronic anticoagulation therapy (e.g., coumadin, dabigatran, apixaban, rivaroxaban or any other agent for any reason). 15. Subject has a platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3. 16. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B. 17. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2 or dialysis at the time of screening.[6] 18. Subject is high risk of bleeding for any reason; has a history of bleeding diathesis or coagulopathy; has had a significant gastro-intestinal or significant urinary bleed within the past six months. 19. Subject has had a cerebrovascular accident or transient ischemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g. aneurysm, arteriovenous malformation, etc.). 20. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used.

[6] Estimated GFR can be based on Modification of Diet in Renal Disease (MDRD) equation or Cockcroft-Gault equation (CCG).

21. Subject has life expectancy < 5 years for any non-cardiac cause or cardiac cause.
22. Subject is in the opinion of the Investigator or designee, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason. This includes completion of Patient Reported Outcome instruments.
23. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.[7]
24. Subject is part of a vulnerable population who, in the judgment of the investigator, is unable to give Informed Consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention.

Angiographic Exclusion Criteria

All exclusion criteria apply to the target lesion(s) or target vessel(s).

1. Lesion which prevents successful balloon pre-dilatation, defined as full balloon expansion with the following outcomes:
    - Residual %DS is a maximum < 40% (per visual estimation), ≤ 20% is strongly recommended.
    - TIMI Grade-3 flow (per visual estimation).
    - No angiographic complications (e.g. distal embolization, side branch closure).
    - No dissections NHLBI grade D-F.
    - No chest pain lasting > 5 minutes.
    - No ST depression or elevation lasting > 5 minutes.
2. Lesion is located in left main.
3. Aorto-ostial RCA lesion (within 3 mm of the ostium).
4. Lesion located within 3 mm of the origin of the LAD or LCX.

[7] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

	5. Lesion involving a bifurcation with a: a. side branch ≥ 2 mm in diameter, or b. side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or c. side branch requiring dilatation 6. Anatomy proximal to or within the lesion that may impair delivery of the Absorb BVS or XIENCE stent: a. Extreme angulation (≥ 90°) proximal to or within the target lesion. b. Excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion. c. Moderate or heavy calcification proximal to or within the target lesion. If IVUS used, subject must be excluded if calcium arc in the vessel prior to the lesion or within the lesion is ≥ 180°. 7. Vessel contains thrombus as indicated in the angiographic images or by IVUS or OCT. 8. Lesion or vessel involves a myocardial bridge. 9. Vessel has been previously treated with a stent at any time prior to the index procedure such that the Absorb BVS or XIENCE would need to cross the stent to reach the target lesion. 10. Vessel has been previously treated and the target lesion is within 5 mm proximal or distal to a previously treated lesion. 11. Target lesion located within an arterial or saphenous vein graft or distal to any arterial or saphenous vein graft.

Lesion Selection

Prior to treatment with the assigned device (Absorb BVS or XIENCE), vessel sizing by visual estimation must be conducted to appropriately match the device to the size of the vessel. Quantitative methods such as on-line QCA, IVUS or OCT can be used if deemed necessary per physician discretion, but are not required. Details on the vessel sizing methods can be found in the Imaging Guidance Document.

Table 1.0 provides the device sizes, the reference vessel diameter (RVD) and lesion length for ABSORB III.

Table 1.0 Absorb BVS and XIENCE Sizes

	Lesion and Device Sizes	
Device	RVD [1]	Lesion Length[1]
Lead-In Absorb BVS (Target lesion)	RVD ≥ 2.75 mm - ≤ 3.25 mm Scaffold diameter: 3.0 mm	Lesion length ≥ 8-≤ 14 mm Scaffold length: 18 mm
RCT Absorb BVS (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Scaffold diameter: 2.5, 3.0 and 3.5 mm	Lesion length ≤ 24 mm Scaffold Length[2]: 8, 12, 18 and 28 mm [3]
RCT XIENCE[5] (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Stent diameter: 2.5, 2.75, 3.0, 3.25 3.5, 4.0 mm	Lesion length ≤ 24 mm Stent Length: 8, 12, 15, 18, 23 and 28 mm [3]
XIENCE (Non-target lesion)	Per IFU (RVD ≥ 2.25 mm - ≤ 4.25 mm can be treated) All available sizes	Per IFU (lesion ≤ 32 mm) [4] All available sizes

[1] Reference vessel diameter (RVD) and lesion length are based on visual estimation.

[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.

[3] For target lesion, planned overlapping is not allowed (i.e. the lesion must be eligible for treatment with a single stent). However, bailout overlapping is allowed if required.

[4] For non-target lesion, planned overlapping allowed.

[5] XIENCE V, XIENCE Prime, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^{X} are used in this study.

A minimum of 2 mm (by visual estimation) of normal or nearly normal reference vessel at both proximal and distal edge should be covered by the device.

Treatment Strategy

- Treatment of a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel.
  - If a single target lesion is treated, it must be treated by the assigned device (Absorb BVS or XIENCE). For Lead-In subject, the target lesion will be treated only with Absorb BVS.
  - If two lesions are treated, possible combinations are as follows:

- Two target lesions:
  - If both lesions satisfy angiographic inclusion/exclusion criteria, then both lesions must be treated by the same device that the subject was randomized to (test device: Absorb BVS or control device: XIENCE),
  - For Lead-In subjects, both target lesions will be treated with Absorb BVS

  OR
- One target lesion and one non-target lesion:
  - If only one lesion satisfies angiographic inclusion and exclusion criteria then this lesion must be treated by the assigned device (test device: Absorb BVS or control device: XIENCE) as a target lesion and the other lesion must be treated by XIENCE as a non-target lesion per the *instructions for use* (IFU).
  - The non-target lesion must be treated first (before randomization) with a XIENCE and the patient may then only be randomized if treatment of the non-target lesion was successful and uncomplicated, defined as final diameter stenosis ≤ 10% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g., distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes. Refer to Figure 2 in Appendix V.
  - For Lead-In subjects, treatment of one target lesion and one non-target lesion is allowed. The target lesion must be treated by Absorb BVS, and the non-target lesion must be treated by XIENCE. The non-target lesion must be treated first and successfully (as defined above) before treating the target lesion with Absorb BVS.

Access Site and Guide Catheter Size:

- Either femoral or radial access may be used.
- A minimum 6F guide catheter or greater must be used during the index procedure per requirements for Absorb BVS implantation (refer to IFU).
  - Minimum guiding catheter compatibility (inner diameter) for Absorb BVS is 0.070”/1.8 mm (6F).
  - Devices (i.e., guide sheaths such as the GuideLiner) that decrease the inner diameter of the guide catheter outside of the

	Absorb BVS minimum guide catheter compatibility must not be used with the Absorb BVS System. Do not insert a 5-in-6, or a 6-in-7 guide sheath into a 6F or 7F guiding catheter, respectively, as doing so will result in an inner diameter that is too small for use with the Absorb BVS. o If a guide sheath is necessary, the inner diameter must meet or exceed the above minimum guiding catheter requirements for Absorb BVS (i.e., only the 7-in-8 GuideLiner provides an adequate inner diameter (0.071" ID), 8F guiding catheter would be required). o For XIENCE, please follow IFU for guiding catheter size. **Baseline Angiogram and Identification of the potential target lesion:** • Assessment of the potential target lesion(s) to be treated must be done to ensure angiographic criteria are met; this must occur prior to pre-dilatation and vessel sizing. **Pre-dilatation of potential target lesion** • Pre-dilatation of the potential target lesions(s) must be performed. • Pre-dilatation must be performed with an angioplasty balloon; cutting or scoring balloons may be used per physician discretion, if the lesion appears to be mildly calcified. • The pre-dilatation balloon should be sized 1:1 to the visually estimated RVD or 0.25 mm smaller than RVD. It cannot be more than 0.5 mm smaller than the visually estimated RVD of the target vessel. If the pre-dilatation balloon is sized 1:1 a non-compliant balloon is strongly recommended. The pre-dilatation balloon must be equal in length or shorter than the planned scaffold/stent length. Important: Full balloon expansion with the pre-dilatation balloon must be achieved before the patient is randomized into the study. If there is any question that the target lesion was not fully dilated or that any significant resistance to expansion from the lesion remains, the lesion should be re-dilated with a non-compliant balloon (sized 1:1 to the RVD) at higher pressure. Absorb BVS or XIENCE must not be implanted in a lesion in which full balloon expansion has not been achieved. • The potential target lesion must continue to meet angiographic criteria following adequate pre-dilatation, to be regarded as "successful pre-dilatation".

	○ For randomized subjects, RVD remains ≥ 2.50 mm - ≤ 3.75 mm, and length of the lesion that will be covered by the device (including any edge dissections) is still ≤ 24 mm. ○ For Lead-In subjects, RVD remains ≥ 2.75 mm - ≤ 3.25 mm, and length of the lesion that will be covered by the device (including any edge dissections) is still ≥8- ≤ 14 mm. ○ Residual %DS is a maximum of < 40% (per visual estimation), ≤ 20% is strongly recommended. ○ TIMI Grade-3 flow (per visual estimation). ○ No angiographic complications (e.g. distal embolization, side branch closure). ○ No dissections NHLBI grade D-F. ○ No chest pain lasting > 5 minutes. ○ No ST depression or elevation lasting > 5 minutes. • For two potential target lesions, the lesion with the higher possibility of failing vessel sizing criteria (per investigator's assessment) should be identified as the first target lesion and pre-dilated first before randomization. ○ If pre-dilatation of the 1st target lesion fails, the patient may not be randomized, and the interactive voice response system (IVRS) must not be called. ○ If the 1st target lesion was successfully pre-dilated and vessel sizing criteria are still met, the IVRS is called to randomize the subject. Once the first lesion is successfully treated[8] with the assigned device (and only at this time), the second target lesion must be pre-dilated, and then treated with the assigned device. ○ If the 1st target lesion was successfully pre-dilated but did not meet vessel sizing criteria, treat as a non-target lesion. Once the first lesion is successfully treated as a non-target lesion, the second lesion must be treated as the target lesion in which successful pre-dilatation and vessel sizing criteria must be met after which IVRS must be called and the target lesion treated per assignment. If 2nd target lesion fails pre-dilatation and vessel sizing criteria, it should be treated as non-target lesion and subject must not be randomized. • Each target vessel and lesion should also be such that the operator believes either the Absorb BVS or XIENCE devices could be delivered to and cross the target lesion without additional lesion

[8] Successful lesion treatment is defined as final diameter stenosis ≤ 30% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g. distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes.

	preparation (e.g. absence of excessive vessel or lesion tortuosity or calcification). **Vessel Sizing** • Following the use of nitroglycerine (at least 100 µg intracoronary nitroglycerine, >150 µg preferred)[9] and successful pre-dilatation of the potential target lesion(s), vessel sizing must be conducted by visual estimation. Quantitative methods such as on-line QCA, IVUS or OCT may be used per physician discretion but are not required, taking into account that QCA tends to under-estimate RVD compared to visual estimation, whereas IVUS tends to over-estimate lumen RVD compared to visual estimation. Follow core laboratory guidelines for the use of each modality. • Prior to randomization, IVUS or OCT can be used to evaluate the vessel if there is question regarding the eligibility of the vessel either before or after pre-dilatation. • A subject must not be randomized in ABSORB III if: o Vessel size or lesion length before or after pre-dilatation does not satisfy eligibility criteria. o Moderate or heavy calcification, tortuosity or other conditions are present proximal or within the target segment, reducing the likelihood that the Absorb BVS or XIENCE can be either delivered to or expanded at the lesion. o Complications and/or adverse events were identified during IVUS or OCT usage (e.g. vessel dissection NHLBI grade D-F).[10] • Table 2.0 provides the guidance of vessel and device sizing during the procedure, which are detailed as the following: o First, assess RVD based on visual estimation o Then, select a pre-dilatation balloon sized 1:1 to RVD or 0.25 mm smaller than RVD. For example, for RVD of 2.5 mm, a pre-dilatation balloon of 2.25-2.5 mm should be used. o Use the size of the inflated pre-dilatation balloon, as well as the results after pre-dilatation, to reassess the RVD for appropriate vessel sizing for the scaffold or stent. If the reassessed RVD after pre-dilatation exceeds the specified range for a specific

[9] If the patient's blood pressure is so low that ≥ 100 ug of nitroglycerine cannot be administered, the patient should not be randomized. It is suggested that ≥200 µg of nitroglycerine be administered if the systolic blood pressure is >140 mmHg. Timing of nitroglycerine administration and pre-dilatation is per physician discretion, but must be before randomization and assessment of scaffold or stent size.

[10] Examples of complications associated with IVUS or OCT: side-branch occlusion, persistent S-T abnormalities, prolonged chest pain, flow limiting dissections etc.

BVS size, the next available size Absorb BVS can be used. For example, if the RVD is reassessed as 2.8 mm after pre-dilatation of a vessel that was believed to be 2.5 mm before pre-dilatation, then implant a 3.0 mm BVS.

- Post-dilatation must always be a non-compliant balloon. Always make sure the non-compliant post-dilatation balloon has a length short enough so it is inflated within the scaffold margins to avoid edge dissection.

Table 2.0 Vessel and Device Sizing[1]

Closest RVD by Visual Estimation	Pre-dilatation Balloon Diameter	Reassessed Closest RVD after Pre-dilatation	Absorb BVS Diameter
2.5 mm	2.25 or 2.5 mm	2.5 mm	2.5 mm
2.75 mm	2.25 – 2.75 mm	2.75 mm	3.0 mm
3.0 mm	2.5 – 3.0 mm	3.0 mm	3.0 mm
3.25 mm	2.75 – 3.25 mm	3.25 mm	3.5 mm
3.5 mm	3.0 – 3.5 mm	3.5 mm	3.5 mm
3.75 mm	3.25 – 3.75 mm	3.75 mm	3.5 mm

Randomization

- Upon successful treatment of the non-target lesion (if any) and completion of successful pre-dilatation and vessel sizing of the first target lesion, interactive voice response system (IVRS) can be called.
- A subject is considered registered and in the ITT population at the time of randomization.
- Lead-In subjects will not be randomized but are assigned to Absorb BVS treatment in target lesion(s).

Lesion Treatment

- The length of the Absorb BVS and XIENCE stent should be selected to allow at least 2 mm of normal or nearly normal reference vessel at each edge.
- If the Absorb BVS cannot reach or cross the lesion or additional lesion preparation is required, the Absorb BVS must be removed and a new Absorb BVS must be introduced after subsequent pre-dilatation(s) with the same sized or larger non-compliant balloon at higher pressure. Note: the Absorb BVS should not be "Dottered" across the lesion if it does not cross easily.

- If the Absorb BVS is unable to reach or cross the target lesion after multiple attempts (maximum of two Absorb BVS; including additional lesion preparation), a XIENCE stent must be used.
- If XIENCE is unable to reach or cross the target lesion after multiple attempts (including additional lesion preparation), the investigator should treat the lesion per standard of care.
- In the case of two target lesions assigned to the Absorb BVS, if the first lesion is unsuccessfully treated with the Absorb BVS the following must occur:
  - First target lesion must be treated with XIENCE. If the treatment of the 1st target lesion is successfully treated with XIENCE, treat the 2nd target lesion with Absorb BVS.
  - If the treatment of the 1st target lesion is unsuccessfully treated with XIENCE, treat the 1st lesion and 2nd lesion per standard of care. The subject must not be treated with Absorb BVS.
  - Every attempt must be made that the two lesion treatments occur at the same index procedure as staged procedures are not allowed. However, if a staged procedure does occur, Absorb BVS must not be used.

  Successful lesion treatment is defined as final diameter stenosis ≤ 30% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g. distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes.
- For Absorb BVS, the scaffold should be deployed slowly, by pressurizing the delivery system in 2 atm increments each over 5 seconds, until the scaffold is completely expanded. Pressure should be maintained for 30 seconds if tolerated by the patient.
- For the Absorb BVS and XIENCE delivery balloon, do not exceed the rated burst pressure (RBP) per the IFU for the individual device.
- Post-dilatation of target lesion or non-target lesion treated with XIENCE should be per standard of care.
- If post-dilatation of the target lesion treated with Absorb BVS is necessary the following guidance is given:
  - A low profile, high pressure, non-compliant, balloon dilatation catheter that has not been previously inflated must be used.
  - The post-dilatation balloon length should be selected such that the balloon stays within the margins of the scaffold so as to avoid an edge dissection.
  - The expanded diameter of the post dilatation balloon must be within the allowable expansion limits of the scaffold. Do not

dilate the Absorb BVS beyond the dilatation limit which is 0.5 mm above the nominal diameter. Doing so may result in scaffold damage. Thus, it is highly recommended that the compliance chart of the non-compliant balloon selected must be carefully reviewed prior to dilatation and an appropriate maximum pressure used to ensure that the scaffold is not over-dilated.

Table 3.0 Scaffold Diameter and Maximum Diameter Limit

Nominal Scaffold Diameter	Post Dilatation Maximum Diameter Limit
2.5 mm	**3.0 mm**
3.0 mm	**3.5 mm**
3.5 mm	**4.0 mm**

- The delivery balloon cannot be removed from the body and reinserted and used for post-dilatation.

- During randomization, if a bailout device is required for a target lesion (e.g., for edge dissection), the same device as the implanted device must be used.
  - Absorb BVS if target lesion is treated with Absorb BVS.
  - XIENCE if target lesion is treated with XIENCE.
  - If a bailout with an Absorb BVS device cannot be delivered to the site of the lesion, the device should be carefully withdrawn and a XIENCE used.
  - If an appropriate size Absorb BVS is not available XIENCE can be used.
- If during the Lead-In phase a bailout is required, the investigator should use an appropriately sized XIENCE stent and not an Absorb BVS.
- Overlap of the bailout stent/scaffold with the implanted stent/scaffold should be 1-2 mm; gaps should be avoided.
- IVUS or OCT guidance may be used as per standard of care in all patients.
- Please refer to the physician training deck for user guidance in handling procedural issues (e.g., difficult in recrossing an implanted scaffold for purposes such as intravascular imaging or post-dilatation if needed).

Imaging Cohort

If subject is in the Imaging Cohort (See **Appendix VI and Imaging Guidance Document** for further details):

	• Post-procedure angiography, IVUS and OCT are required based on respective imaging groups. • If post-dilatation was performed, post-procedure imaging must be conducted following last balloon inflation. • 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.
Antiplatelet[11] Therapy	**Antiplatelet Medication Loading Dose:** • Aspirin: Subjects must receive a loading dose of ≥ 300 mg of aspirin within 24 hours before the procedure, regardless of whether the patient was previously taking aspirin • Adenosine diphosphate (ADP) antagonist: either clopidogrel, prasugrel or ticagrelor may be used as per standard of care and per label indications. A loading dose of the ADP antagonist must be given within 24 hours prior to the index procedure (preferred) but in all cases no greater than 1 hour after the end of the procedure. o Clopidogrel: a peri-procedural loading dose 600 mg is required o Prasugrel: a peri-procedural loading dose of 60 mg is required o Ticagrelor: a peri-procedural loading dose of 180 mg is required. • For patients with recent ACS prior to admission, it is strongly recommended that the loading dose be given at least 6 hours before the procedure (clopidogrel 600 mg), or 1 hour prior to the procedure (prasugrel 60 mg or ticagrelor 180 mg), but in all cases no greater than 1 hour after the end of the procedure. • The prasugrel or ticagrelor loading dose may be omitted for those subjects on chronic prasugrel (5 or 10 mg daily) or ticagrelor (90 mg twice daily) for ≥ 7 days prior to the index procedure. For patients maintained on chronic clopidogrel, the loading dose of the ADP antagonist must be administered. A loading dose of prasugrel or ticagrelor may be safely given to patients maintained on chronic clopidogrel therapy, or even in those in whom a clopidogrel loading dose was recently administered. • Ticlopidine may be used as a substitute at a dose in accordance with standard hospital practice only if the subject develops

[11] ABSORB III will allow the use of FDA approved P2Y12 inhibitors. Loading and maintenance dosages of all P2Y12 inhibitors should follow respective prescribing information. If outside the US, country specific approvals are allowed.

	hypersensitivity or intolerance to clopidogrel, prasugrel, or ticagrelor. • Refer to respective prescribing information for ADP Antagonist for further details regarding loading practice. **Antiplatelet Medication Post-Procedure Daily Dose:** • All subjects will be maintained at a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients*) or 90 mg twice daily of ticagrelor for a minimum of 12 months following the procedure. • All subjects must receive ≥75 to ≤100 mg of aspirin daily through 5 years follow-up during the study and should continue to take aspirin indefinitely. *For prasugrel subjects < 60 kg in weight or ≥ 75 years of age a maintenance dose of 5 mg per day for 12 months is allowable. Patients with prior stroke or TIA should receive clopidogrel or ticagrelor, not prasugrel. Refer to respective prescribing information for ADP antagonist for further details regarding maintenance dose.
Cardiac Biomarker Collection	**Between Baseline and Discharge** • Pre-procedure CK and CK-MB draw* • First post-procedure CK and CK-MB draw at 6 to 12 hours post-procedure. • Second post-procedure CK and CK-MB draw at 18-24 hours post-procedure, or at the time of discharge as long as discharge is at or after 16 hours post-procedure.** • If either of the post-procedure CK-MB levels are ≥ 3 x ULN, serial CK and CK-MB levels must be drawn until they are falling. • A 12 lead ECG must be obtained at baseline and between 30 and 90 minutes post procedure * If the patient has stable coronary artery disease, the pre-procedure level can be obtained during procedure but prior to stent/scaffold deployment. If the patient has a recent acute coronary syndrome, the pre-procedure level must be obtained prior to the procedure and the CK-MB shown to be within normal limits prior to the patient being randomized. CK and CK-MB levels are required at all time points. If troponin is collected at the pre-procedure or post-procedure time points, this should also be documented in the electronic case report forms.

	** For hospitals required to discharge stable subjects prior to 16 hours, the subject may be discharged but will have to return to the enrolling institution for their second biomarker draw.
Primary Analytical Population	The primary analysis population will be the ITT population.

1. INTRODUCTION

The ABSORB III Randomized Controlled Trial (RCT) evaluates the safety and effectiveness of the Abbott Vascular Absorb™ Bioresorbable Vascular Scaffold (BVS) System[12]. The Absorb BVS System[13] will be compared to the commercially approved, control stent XIENCE. ABSORB III also includes a Lead-In phase and an Imaging Cohort and includes a maximum of 220 sites in the United States and outside the United States. The ABSORB III primary endpoint is target lesion failure (TLF) (cardiac death, target vessel myocardial infarction and ischemia-driven target lesion revascularization) at 1 year.

The Absorb BVS used in the ABSORB III trial is the Absorb BVS System manufactured in Temecula California [Absorb BVS System (mfg TEM)][13]. Clinical trials in the ABSORB Clinical Program have utilized the Absorb BVS System manufactured in Mountain View California (mfg MTV). The Absorb BVS System (mfg TEM) introduces eight additional sizes to the Absorb BVS System product matrix for ABSORB III (Refer to Table 4.1). Concurrent with the manufacturing site transfer, Abbott Vascular has implemented design and manufacturing enhancements to increase product robustness and product ease of use (Refer to Section 2.1.4.6). Hereinafter, Absorb BVS System (mfg TEM)[13] will be known as Absorb BVS, unless specified.

ABSORB III is a prospective, randomized (2:1 Absorb BVS to XIENCE), single-blind, multi-center trial, registering approximately 2250 subjects. This is the pivotal trial to support the US PMA approval of Absorb BVS. The primary objective of ABSORB III is to evaluate the safety and effectiveness of the Absorb BVS System compared to the XIENCE in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. The primary endpoint data from this trial will be based on approximately 2000 subjects and will support label claims of non-inferiority of Absorb BVS as compared to XIENCE in 1-year TLF. The ABSORB III will also include a Lead-In Phase and an Imaging Cohort. The ABSORB III will also support a diabetes indication for Absorb BVS.

Lead-In Phase

A non-randomized, single-arm, open label group of up to 50 subjects treated with Absorb BVS at up to 35 US sites. The objective of the Lead-In is to evaluate the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice. The Lead-In Phase will enroll/register subjects prior to the randomization in ABSORB III.

Imaging Cohort

A prospective, randomized (2:1 Absorb BVS to XIENCE), single-blind, multi-center cohort, registering approximately 200 subjects. The 200 subjects are separate from the 2000 subjects included in the primary endpoint analysis. The objective of the Imaging Cohort is to evaluate long-term vascular function and patency of the Absorb BVS treated segments compared to XIENCE treated segments. Data from two powered secondary endpoints from this cohort will

[12] The commercially approved CE marked device will be used in geographies where it is commercially available.
[13] The Absorb™ Bioresorbable Vascular Scaffold (BVS) System is the trade name for this product. During the course of development, multiple product names were used to describe this product including, Bioresorbable Vascular Scaffold (BVS) System, Bioabsorbable Vascular Stent, BVS Everolimus Eluting Coronary Stent System (EECSS), Abbott Vascular Bioabsorbable Device (AVBD) EECSS, BVS Cohort A (used in the ABSORB Cohort A trial) and BVS Cohort B (used in the ABSORB Cohort B trial).

support label claims of superiority of Absorb BVS as compared to XIENCE specific to vasomotion and late lumen enlargement.

After the completion of Lead-In Phase, enroll/registration of the 2000 subjects for the primary analysis and the 200 subjects in the Imaging Cohort will begin. All trial elements will apply to Lead-In Phase and the Imaging Cohort, unless otherwise specified.

Figure 1.1 provides the complete ABSORB III design.

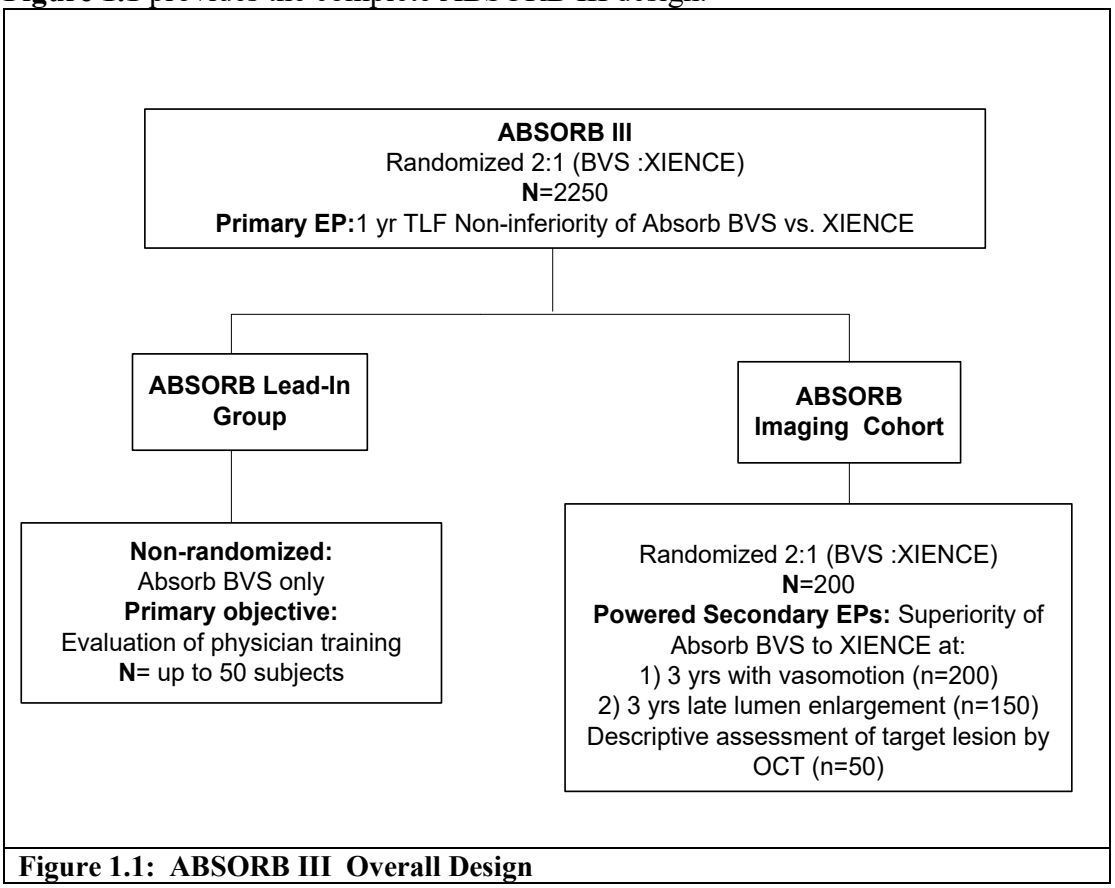


Figure 1.1: ABSORB III Overall Design

In addition, all 2,000 primary analysis subjects in ABSORB III will complete patient-reported outcome (PRO) self-administered questionnaires at baseline, 30 days, 1, 2 and 3 years (EQ-5D, SAQ, RDS, GAD-7) and at 5 years (EQ-5D, SAQ).

The Lead-In Phase allows the treatment of up to two *de novo* native coronary artery lesions in different epicardial vessels with RVD ≥ 2.75 mm to ≤ 3.25 mm and lesion lengths ≥ 8 to ≤ 14 mm. All other subjects in ABSORB III unless specified will receive treatment of up to two *de novo* native coronary artery lesions in different epicardial vessels with RVD ≥ 2.5 mm to ≤ 3.75 mm and lesion lengths ≤ 24 mm.

All subjects (including Lead-In) will be screened per the protocol inclusion and exclusion criteria and registered subjects will have clinical follow-up at 30 days, 180 days, and 1, 2, 3, 4, and 5 years. Subjects in the Imaging Cohort will receive imaging follow-up at 3 years for angiography and IVUS or OCT.

2. BACKGROUND INFORMATION

2.1 Summary of Investigational Device

2.1.1 Name of the Investigational Device

The investigational device to be used in this trial is the Absorb BVS System[14]. In this protocol, the investigational scaffold or test device is referred to as "the Absorb BVS". The Absorb BVS System is manufactured by Abbott Cardiovascular Systems, Inc., California, an affiliate of Abbott Vascular, Inc.

2.1.2 Intended Indication

The Absorb Bioresorbable Vascular Scaffold (BVS) is a temporary scaffold that will fully resorb over time and is indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus, with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm.

2.1.3 Absorb BVS Features

The Absorb BVS is a bioresorbable balloon-expandable scaffold with a drug and bioresorbable polymer coating. After implantation, the scaffold supports the vessel mechanically for an appropriate period. It is then resorbed in the body and the polymer material becomes undetectable over time. In contrast, currently available commercial coronary stents are made of metal, which resides permanently in the body.

The first therapeutic catheterization for coronary artery stenosis was performed by Andreas Gruentzig in 1977. Percutaneous transluminal coronary angioplasty (PTCA) with a balloon was the first therapy which became commonly performed. After a vessel is treated by PTCA restenosis, which may require additional treatment, can occur due to 1) acute recoil, 2) remodeling, and/or 3) neointimal proliferation. A stent can minimize the occurrence of recoil and remodeling by mechanically supporting the vessel lumen. However, the vessel support is required only for approximately three - six months to prevent recoil and remodeling [2-4] , and an implanted stent after this period may no longer be necessary.

The Absorb BVS is designed to revascularize obstructed coronary arteries and ultimately restore the implanted vessel to an unconstrained state potentially capable of dilating and contracting in response to changes in blood flow requirements. The performance of the Absorb BVS is described by three phases that span its lifecycle, namely revascularization, restoration, and resorption (**Figure 2.1**). These stages parallel the well-known description of PLA degradation, whereby molecular weight, strength, and mass loss decrease progressively one after the other [5]. It is important to note that **Figure 2.1** reflects design objectives rather than the explicit performance of the Absorb BVS.

[14] The commercially approved CE marked device will be used in geographies where it is commercially available.

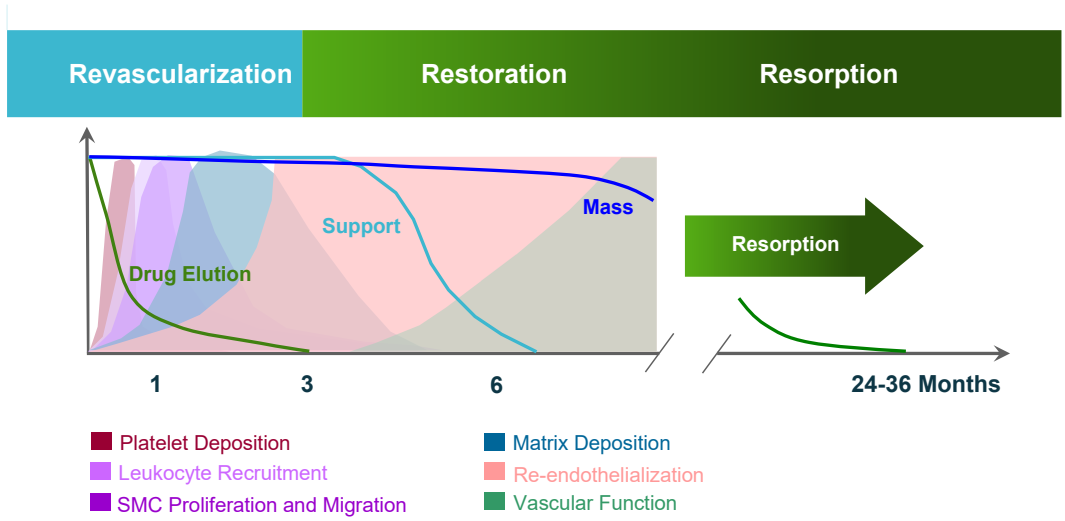


Figure 2.1: Schematic Drawing of the Minimum Design Objectives for the Three Phases of Absorb BVS performance

The revascularization phase is the first phase, in which the Absorb BVS most closely mimic the design considerations of metallic DES. Specifically, it is necessary that the device be deliverable to the target site, the scaffold deploy with a minimum of recoil and provide adequate acute radial strength, and the therapeutic agent be delivered to abluminal tissue at a controlled rate. The critical performance attribute of the Absorb BVS during the revascularization stage is to provide luminal support for the period of time necessary for the vessel lumen to stabilize. Percutaneous transluminal coronary angioplasty (PTCA) data for mean lumen diameter and percent diameter stenosis suggest that this time scale is approximately three months [4] .

The restoration phase characterizes the transition from active support of the lumen to a passive implant consisting of discontinuous structural elements. The aggregate of luminal scaffolding and structural continuity is represented by the curve labeled "Support" in **Figure 2.1**. Significantly, when the state of structural discontinuity is reached, constriction and dilation of the vessel should no longer be inhibited by the scaffold. The manner in which the Absorb BVS loses radial strength is a principal design consideration, as it must not only lose radial strength but also become structurally discontinuous still later into the degradation process. Because of the probable dependence upon patient physiology and disease state, the boundary between the end of the restoration phase and the resorption phase is nebulous, as depicted in **Figure 2.1**.

After the Absorb BVS becomes structurally discontinuous, it ceases to perform any scaffolding role and may be considered functionally inert. The sole remaining design objective of the remaining implant is that it be resorbed in a benign fashion. The Absorb BVS polymer continues to be degraded through hydrolysis until molecules are sufficiently small that they can diffuse through the implant then dissolve into the blood stream and surrounding tissue. The ultimate byproduct of PLA is lactic acid, which is readily converted to lactate. Lactate is in turn metabolized into CO_2 and H_2O via the Krebs Cycle and also serves as a source of energy in anaerobic metabolism [6-8].

2.1.4 Description of the Investigational Device

The Absorb BVS System is a balloon-expandable, drug-eluting bioresorbable vascular scaffold, where the components of the Absorb BVS System include:

- A bioresorbable poly(L-lactide) (PLLA) scaffold backbone.
- A coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly(D,L-lactide) (PDLLA).
- Four platinum marker beads, two each embedded at the proximal and distal ends of the scaffold for radiopacity.
- A delivery system similar in design, materials, and performance to that of the MULTI-LINK VISION® Rapid Exchange (RX) Coronary Stent System (CSS) and MULTI-LINK MINI VISION® CSS (P020047 and supplements).

2.1.4.1 Polylactide

Bioresorbable polymers have been the subject of extensive scientific research and commercial development in fields as diverse as food packaging and biomedical devices. Polylactide (PLA) and its copolymers have a long history of use in medical devices starting with bioresorbable sutures in the 1960s. These polymers are now used in a wide range of bioresorbable implants, including: orthopedic devices such as plates, pins and screws; drug delivery systems such as solid implants and gel based systems; suture anchors; peripheral bioabsorbable stents; and surgical mesh and clips. Prior experience with bioresorbable polymers in human applications includes the Angio-Seal™ vascular closure device (St. Jude Medical) [9], BioMatrix™ drug-eluting stent (Biosensors International Ltd.) [10], the Bio-Corkscrew™ full-threaded suture anchor (Arthrex, Inc.) [11], (Longo) and the Igaki-Tamai® bioabsorbable stent (Kyoto Medical Planning Co Ltd.) [12]. The Angio-Seal device, fabricated in part from poly(lactide-*co*-glycolide) (PLGA), reveals that the release of degradation products from a bioresorbable device is well tolerated by a blood vessel. The BioMatrix DES contains a PDLLA coating, which controls the drug release into the coronary tissue and bloodstream. The Bio-Corkscrew suture anchor exemplifies the safe use of PDLLA to fix sutures (soft tissue) to bone in rotator cuff repair. The Igaki-Tamai stent, made completely from PLLA, demonstrates the intrinsic safety of that material when used in coronary arteries, and this stent received CE mark for peripheral vascular application. Finally, the Absorb BVS System is currently CE Marked as a temporary scaffold indicated for improving coronary luminal diameter that will eventually resorb and potentially facilitate normalization of vessel function in patients with ischemic heart disease due to *de novo* native coronary artery lesions.

PLA is a member of the aliphatic polyester family of materials. The lactide monomer from which PLA is synthesized is a cyclic di-ester of lactic acid, which is a chiral molecule with two optical isomers, L-lactic acid and D-lactic acid. When lactide is prepared from a racemic mixture of lactic acid, one obtains three isomers, namely D-lactide, L-lactide, and *meso*-lactide. The *meso*-lactide isomer is readily separated from the other two isomers. Polymerization of pure L-lactide or D-lactide leads to the optically active and crystallizable PLLA and poly(D-lactide) (PDLA), respectively. Polymerization of a racemic mixture of L-lactide and D-lactide leads to the

optically inactive and amorphous PDLLA, which is a random copolymer containing equal numbers of L- and D-lactide monomer subunits.

PLLA is a semicrystalline polymer whose degree of crystallinity and crystalline microstructure are dependent upon the thermal and deformation history during processing. The high tensile strength and modulus of PLLA make it suitable for load bearing applications. PLLA has a maximum crystallinity of approximately 70%, a melting temperature (T_m) of 170 - 180°C, and a glass transition temperature (T_g) of 55 - 65°C [13, 14].

PDLLA is a random copolymer derived from an equimolar mixture of D- and L-lactide. PDLLA is characterized by a lower tensile strength and higher elongation than PLLA due to its amorphous structure. Because amorphous polymers lack crystalline structure, they do not have melting temperatures but instead begin to flow at temperatures in excess of T_g [13, 14].

2.1.4.2 PLLA Scaffold

The Absorb BVS is a bioresorbable balloon-expandable scaffold with a drug and bioresorbable polymer coating. The Absorb BVS is fabricated from PLLA and is comprised of a series of circumferentially oriented sinusoidal rings connected by linear links (**Figure 2.2**). The design is based upon the same principles as metallic balloon expandable stents (MULTI-LINK family of coronary stent systems) with permanent deformation of the device being achieved by permanent deformation of the ring structure. Two permanent platinum markers are embedded at each end ring to enable fluoroscopic visualization.

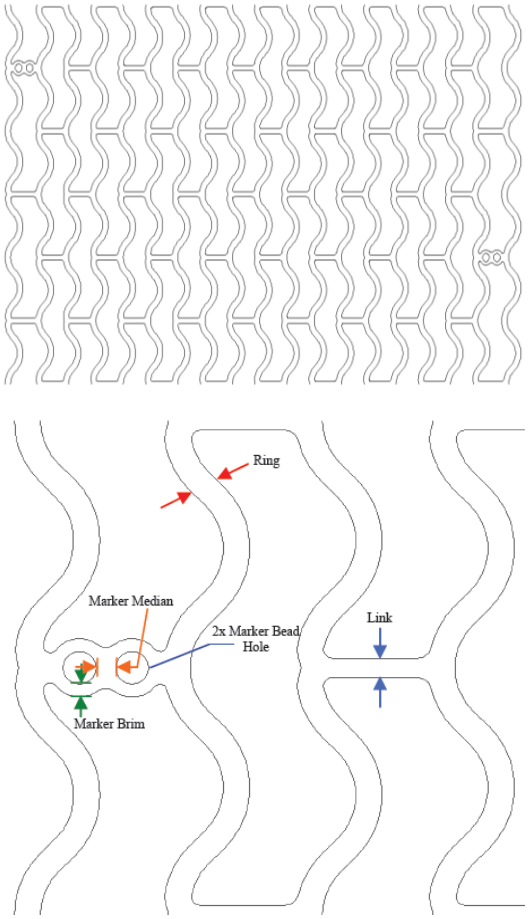


Figure 2.2: BVS Strut Pattern

2.1.4.3 Absorb BVS Bioresorbable Coating

The Absorb BVS bioresorbable polymer drug coating is a single drug/polymer matrix layer comprised of the amorphous random copolymer PDLLA, which contains and controls the release of the drug, everolimus. Everolimus is an anti-proliferative (Afinitor, Novartis Pharmaceuticals Corp.) that is blended with PDLLA in a 1:1 (w:w) proportion and applied to the entire surface (i.e., sidewalls, luminal and abluminal) of the PLLA scaffold.

Neither a primer coat nor a topcoat layer is utilized for the Absorb BVS. A study has shown that the amount of drug transferred to the balloon (Pebax polymer) is less than 0.01 wt% of the label claim for total content.[15]

2.1.4.4 Everolimus

Everolimus [40-O-(2-hydroxyethyl)-rapamycin], which is provided to Abbott Vascular by Novartis Pharmaceuticals Corporation, is a novel semisynthetic macrolide immunosuppressant,

[15] RPT2068797 Drug Content Along the Length of BVS Stents

obtained through chemical modification of Rapamycin. Rapamycin (INN: sirolimus) is a secondary macrolide metabolite that is produced by certain actinomycete strains. The oral formulation of everolimus[16] known as Certican® (Novartis Pharmaceuticals Corporation), outside the United States and as Zortress® in the U.S., is for the prevention of organ transplant rejection. Novartis Pharmaceuticals Corporation has granted Abbott Vascular the right to reference Certican's IND 52,003, NDA No. 21-560 and NDA No. 21-638. Additionally, the oral formulation of everolimus known as Afinitor® (Novartis Pharmaceuticals Corporation) is approved as of March 30, 2009, in the U.S. for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Everolimus has also been used in similar dosing on the CE Marked and FDA approved XIENCE permanent vascular implants..

The nominal drug dose per scaffold size of BVS and XIENCE is given in **Table 2.1**.

[16] AFINITOR Highlights of Prescribing Information, Novartis Pharma Stein AG, March 2009; Zortress Prescribing Information, Novartis Pharma Stein AG, 2010; Certican Investigator's Brochure Novartis. October 2, 2009.

Table 2.1 Nominal Drug Dose Comparisons

Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	XIENCE PRIME, Xpedition, Alpine, and Pro^{X}†† Nominal Drug Dose (µg)	XIENCE V and Pro Nominal Drug Dose (µg)	Cohort A Device* Nominal Drug Dose (µg)	Absorb BVS System ** (mfg MTV) Nominal Drug Dose (µg)	Absorb BVS System† (mfg TEM) Nominal Drug Dose (µg)
2.25, 2.5, 2.75, 3.0, 3.25	8	40	37	NA	NA	76
3.5, 4.0		50	53	NA	NA	NA
2.25, 2.5, 2.75, 3.0, 3.25	12	60	56	98	NA	114
3.5, 4.0		75	75	NA	NA	135
2.25, 2.5, 2.75, 3.0, 3.25	15	74	75	NA	NA	NA
3.5, 4.0		91	98	NA	NA	NA
2.25, 2.5, 2.75, 3.0, 3.25	18	88	88	148	160	181
3.5, 4.0		116	113	NA	NA	197
2.25, 2.5, 2.75, 3.0, 3.25	23	109	113	NA	NA	NA
3.5, 4.0		141	151	NA	NA	NA
2.25, 2.5, 2.75, 3.0, 3.25	28	137	132	NA	235	276
3.5, 4.0		174	181	NA	NA	308

* In the ABSORB BVS Cohort A trial, the Cohort A device was only available in 3.0 mm diameter and 12, 18 mm length.

** In the ABSORB BVS Cohort B trial, the Absorb BVS System (mfg MTV) was only available in 3.0 mm diameter and 18 mm length.

† In ABSORB III, the BVS System (mfg TEM) will only be available in 2.5, 3.0, 3.5 mm.

†† The 3.25 mm is only available with the XIENCE Xpedition, Alpine, and Pro^{X}.

2.1.4.5 Delivery System

The Absorb BVS delivery system is similar in design, materials, and performance to that of MULTI-LINK VISION RX CSS (P020047 and supplements), which is commercially approved in more than 80 countries, including the United States, Canada and European Union. That delivery system is also similar to that of XIENCE V RX Stent System (P070015) and MULTI-LINK RX ZETA CSS (P070020/S042).

Like other Abbott Vascular RX Coronary Stent Systems and Coronary Dilatation Catheters, the Absorb BVS delivery system combines a single lumen proximal shaft with a dual lumen mid-shaft and a co-axial lumen distal shaft to create the rapid exchange capability. The single lumen proximal shaft connects the intermediate/distal shaft with the inflation port of the catheter. The guide wire exit notch is located at the proximal end of the junction between the intermediate shaft and the mid-shaft support. The annular space between the distal outer member and the central distal lumen provides a fluid passage path from the proximal lumen to the balloon. The shaft of the catheter, the tip, and tapers of the balloon are coated with HYDROCOAT Hydrophilic Coating. The overall length of the catheter is 143 cm.

Two radiopaque balloon markers are located on the distal segment of the inner member and are positioned to mark the working length of the balloon. The scaffold is mounted such that the markers reflect the expanded scaffold length. The radiopaque markers aid in positioning the scaffold fluoroscopically and accurately positioning the delivery system for post-deployment dilation, if necessary. Two non-radiopaque markers are attached to the proximal end of the shaft of the Absorb BVS delivery system, specifically 95 cm and 105 cm proximal to the distal tip. These two markers indicate when the distal tip of the catheter exits the tip of a brachial or femoral guiding catheter, respectively.

A single arm adapter is attached to the proximal end of the catheter and accesses the inflation/deflation lumen. The proximal shaft is thermally bonded to a nylon adaption cup, which is mechanically sealed to the single arm adapter with a polycarbonate nosepiece. The nosepiece is threaded onto the single arm adapter, and these are bonded together with methylene chloride.

A 0.014 inch (0.36 mm) or smaller diameter guide wire can be used in the guide wire lumen. The guide wire exits the guide wire lumen at the guide wire exit notch, which is formed at the junction of the mid-shaft and the intermediate shafts. Proximal to this point, the guide wire runs externally alongside the proximal shaft of the catheter.

2.1.4.6 Absorb BVS Device Comparisons

During development of the current Absorb BVS System, the product has undergone multiple design, process, and manufacturing control changes. The scaffold pattern was modified from the initial hourglass pattern used in the Absorb Cohort A trial to a sinusoidal rings with three links design (based on the MULTI-LINK family of patterns) for the Absorb Cohort B trial. The Absorb Cohort B pattern, manufactured in the Mountain View facility and also described here as Absorb BVS System (mfg MTV), has been further improved as part of the transition to manufacturing at Abbott Vascular's Temecula facility. The Absorb BVS (mfg TEM) scaffold pattern remains based on the MULTI-LINK family of patterns, but with increased overall crest and bar arm length, which creates a larger theoretical maximum expanded

diameter. Optimization of the scaffold strut width and thickness maintains radial strength while balancing other functional attributes. The Absorb Cohort A BVS System and the Absorb BVS System (mfg MTV and mfg TEM) share the same material composition, drug dose density (100 $\mu g/cm^2$), and drug release profiles. Absorb BVS (mfg TEM) has a slightly increased surface area and thus a slight increase in total drug dose as compared to the same size Absorb BVS (mfg MTV). Additional device sizes were designed for the Absorb BVS System (mfg TEM). The Absorb BVS (mfg MTV) and Absorb BVS (mfg TEM) delivery systems are identical in materials, with minor dimensional adjustments to accommodate the Absorb BVS, to that of MULTI-LINK VISION RX CSS, which is commercially approved in more than 80 countries, including the United States, Canada, and within the European Union.

The principles of operation for the Absorb BVS (mfg MTV) and the Absorb BVS (mfg TEM) are identical, i.e. the Absorb BVS, regardless of site of manufacture or scaffold pattern, is designed to revascularize obstructed coronary arteries and ultimately restore the implanted vessel to an unconstrained state. The Absorb BVS System (mfg TEM) meets or exceeds all the essential performance requirements of the Absorb BVS System (mfg MTV) and is available in sizes shown in Table 2.2.

Table 2.2 Absorb BVS System Product Size Matrix

		Product Length (mm)		
Product Diameter (mm)	**8**	**12**	**18**	**28**
2.5	X	X	X	X
3.0	X	X	X	X
3.5		X	X	X

A = Anticipated additional size.
X = Size currently available.

Please note that the commercially approved CE marked 23mm Absorb BVS device will not be used in this study.

2.1.5 Description of the Control Device

The commercially available XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^X [17] Stent Systems will serve as the control device. Hereinafter, these devices will be called "XIENCE" in this trial.

XIENCE Pro is a rebranding (re-labelling) of the commercially available XIENCE V and XIENCE PRIME. XIENCE Pro^X is a rebranding of the commercially available XIENCE Xpedition. XIENCE Pro and XIENCE Pro^X are only approved for use outside the US.

The XIENCE is composed of a drug coated stent and balloon expandable delivery system. The drug coating is composed of two polymers and the anti-proliferative drug everolimus. The delivery system used in this trial utilizes the same principle of operation as other Abbott Vascular Rapid Exchange (RX) coronary stent systems and coronary dilation catheters. The XIENCE is fabricated from a single piece of medical grade L-605 Cobalt Chromium (CoCr)

[17] For geographies where these devices are commercially available, the investigational sites may use only their locally approved devices.

alloy. This alloy can be formed into thinner stent struts than traditional stainless steel stents, and provides a more flexible, low delivery system profile while maintaining adequate radiopacity and strength. For more details on the XIENCE please refer to the XIENCE V, XIENCE PRIME, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^{X} IFUs.

2.1.6 Investigational Device Accountability

The Sponsor will ship the investigational devices (Absorb BVS System) to the Primary Investigator (or designee) only at each site. In geographies using the commercially available CE marked device, the investigators will acquire the product through their normal commercial vendors. The Primary Investigator will maintain adequate records of the receipt and disposition of the investigational device, including part number and serial number, date implanted, patient identification [ID] number and implanting physician. An Inventory Accountability Report will be generated for this purpose. In geographies not using the commercially available CE marked device, any unused investigational devices will be returned to the Sponsor and a completed Inventory Accountability Report will be generated for the site when the enrollment phase of the study is complete. The Inventory Accountability Report must document the disposition of all investigational devices including those that have been returned to the Sponsor. Use of any investigational device outside of the protocol (e.g., compassionate use) is strictly forbidden and may constitute grounds for removal of the investigator/site from the study. In geographies using the commercially available CE marked device, the commercial device may be used in non-trial patients. The sites will manage the XIENCE and the commercially available CE marked Absorb BVS device supplies for this trial without sponsor oversight and the device should be used in accordance with the IFU. In sites using commercially available CE marked devices (XIENCE and Absorb BVS), the primary investigator will maintain records of device usage for the study subjects. The records will contain device part number and serial number, date implanted, patient identification number, and implanting physician.

2.1.7 Summary of Pre-Clinical Studies

A comprehensive series of animal studies have been conducted to demonstrate safety of the Absorb™ Bioresorbable Vascular Scaffold (BVS) System[18]. The studies collectively evaluate the BVS Cohort A device and the Absorb BVS System manufactured in Mountain View [Absorb BVS System (mfg MTV)], and the Absorb BVS System manufactured in Temecula [(Absorb BVS System (mfg TEM)], the latter of which is the investigational device to be used in this clinical trial. The BVS Cohort A device and the Absorb BVS (mfg MTV and mfg TEM) share the same materials composition, drug dose density, and drug release profiles. Absorb BVS (mfg TEM) has a slightly increased surface area and thus a slight increase in total drug dose (13% based on 2.5/3.0 x 18 mm). Other subtle changes involved in the manufacturing site transfer for optimization and scale-up to improve consistency, throughput, yields, and overall process robustness have no impact on the preclinical performance of the Absorb BVS System. Consistent preclinical safety has been demonstrated among the BVS Cohort A device (1 to 48 months), the

[18] The Absorb™ Bioresorbable Vascular Scaffold (BVS) System is the trade name for this product. During the course of development, multiple product names were used to describe this product including, Bioresorbable Vascular Scaffold (BVS) System, Bioabsorbable Vascular Stent, BVS Everolimus Eluting Coronary Stent System (EECSS), Abbott Vascular Bioabsorbable Device (AVBD) EECSS, BVS Cohort A (Gen. 1.0) (used in the ABSORB Cohort A trial) and BVS Cohort B (Gen.1.1) (used in the ABSORB Cohort B trial).

Absorb BVS (mfg MTV) (3, 28, 90, 180 days and 12, 18, 24, and 30 months), and the Absorb BVS (mfg TEM) (28, 90, and 180 days).

Experience in the preclinical setting has been cumulative among these devices because of the similarities they share. Studies conducted using the Cohort A device include a 90-day pharmacokinetics study, a safety study at 28 and 90 days, a safety study from 1 to 48 months, and a degradation study at 10, 12, 18, 24 and 36 months. These studies were conducted in porcine coronary arteries. Additionally, a 3 to 36 months safety study was conducted in rabbit iliac arteries. Studies conducted for the Absorb BVS (mfg MTV) include an up to 90-day pharmacokinetics study; two safety studies with collective evaluations at 3, 28, 90, 180 days and 12, 18, 24, and 30 months; a 28-day and a 90-day overlap safety study; and two *in vivo* degradation studies with collective evaluations at 28, 90, and 180 days and at 12, 18, 24, and 30 months. These studies were conducted in porcine coronary arteries. Studies conducted for the Absorb BVS (mfg TEM) include an up to 90-days pharmacokinetics study and three safety studies (28, 90, and 180 days).

With respect to pharmacokinetics, studies conducted demonstrate bioequivalence of Absorb BVS (mfg MTV) and Absorb BVS (mfg TEM) with 78-79% of everolimus being released at 28 days and 96% at 90 days. Bioequivalence of the drug release profiles was not only demonstrated between the Absorb BVS (mfg MTV) and the Absorb BVS (mfg TEM), but also between the Absorb BVS (mfg MTV and mfg TEM) and the XIENCE V Everolimus Eluting Coronary Stent. Therapeutic concentrations of everolimus were maintained in target vessels for at least 28 days following implantation of Absorb BVS (mfg MTV and mfg TEM). A systemic safety profile of Absorb BVS (mfg MTV and mfg TEM) was also demonstrated in the PK studies.

Safety of the BVS Cohort A device was demonstrated in two studies in porcine coronary arteries using CYPHER (1 to 48 months) and VISION (28, 90 days) controls and in rabbit iliac arteries using a CYPHER control (3 to 36 months). Safety of the Absorb BVS (mfg MTV) was confirmed in single configuration at 3, 28, 90, 180 days and at 12, 18, 24, and 30 months and in overlapping configuration at 28 and 90 days in porcine coronary arteries using XIENCE V (single and overlapping) as the respective control. Absorb BVS (mfg TEM) demonstrated safety in porcine coronary arteries at 28, 90, and 180 days. Collectively, comparable safety to the respective control device(s) was demonstrated through the maintenance of lumen patency, sequestration of struts in a benign neointima, near to complete endothelialization by 28 days (single) and 90 days (overlapping), and inflammation that was within pre-established safety acceptance criteria. Luminal thrombosis, medial necrosis, and medial thinning were not observed in any of these studies. From 24 to 48 months in arteries implanted with BVS Cohort A device, resorption sites representing pre-existing struts were benignly integrated into the arterial wall. Degradation studies conducted for Absorb BVS (mfg MTV) demonstrate up to 74% resorption by 30 months with no adverse responses, and Absorb BVS (mfg TEM) is expected to have similar *jn vivo* degradation based on the similar material composition and *in vitro* degradation rates through 180 days shared by Absorb BVS (mfg MTV) and Absorb BVS (mfg TEM).

The Absorb Cohort A BVS System and the Absorb BVS (mfg MTV and mfg TEM) demonstrate commensurate safety and function at revascularization, which relates to both luminal support and everolimus suppression of neointimal hyperplasia. Collectively the results from this series of animal studies support the validity of commencing clinical studies using the Absorb BVS in this trial.

2.1.8 Previous Clinical Studies

While drug-eluting metallic stents have significantly reduced restenosis rates after PCI, longer treatment areas covered by metallic stents may preclude surgical revascularization. Further, the absence of a permanent stent may favor maintained luminal patency associated with remodeling. Additionally, bioresorbable scaffolds can act as a vehicle for local therapy and are amenable to non-invasive cardiovascular imaging. There is angiographic and clinical evidence from a small number of recent studies demonstrating that the bioresorbable stent/scaffold is associated with low restenosis and adverse event rates. However, due to the limited number of studies, small sample size, and short-term follow-up, long-term studies are warranted evaluating the bioresorbable scaffold.

2.1.8.1 Bioresorbable Stent/Scaffold

Early Bioresorbable Stent/Scaffold Prototypes

The first bioresorbable stent was developed at Duke University in the early 1980s. The stents made from PLLA were implanted in canine femoral arteries. The strut surface was completely endothelialized at 2 weeks and the vessels remained patent at 12 weeks post-implantation. No inflammatory response and no thrombosis were observed [15, 16]. This technology subsequently was acquired by Guidant Corporation, and now Abbott Vascular.

Igaki-Tamai Stent

Tamai *et al* were the first group to provide clinical investigation data with PLLA implant in humans. A prospective, unblinded Clinical Investigation was carried out to assess the feasibility and safety of the Igaki-Tamai stents. Fifty subjects electively underwent percutaneous coronary artery intervention (PCI) for coronary artery stenosis with the Igaki-Tamai stent over a period of 19 months. There were 63 lesions in Japan that were enrolled in the study from September 1998 to April 2000 in which a total of 84 Igaki-Tamai stents were received. Angiographic follow-up was performed for the first 19 lesions at 3 months and 6 months and the percent diameter stenosis (%DS) was 33% at both of the follow-up time points [12]. This was comparable to the %DS at 6 months post-implantation of BMS (29.2% in VISION stent; 34.6% in TETRA stent). Clinical follow-up was performed at up to 4 years, and MACE rate at 4 years was reported as 18%[17]. Stent struts were not visible during IVUS follow-up at three years [18]. Additionally, one subject was followed at 9 years and good patency was observed by optical coherence tomography OCT (**Figure 2.3**) [19]. Recently, 10 year plus follow-up data was presented on the 50 patients that received Igaki-Tamai stents. Survival rates for freedom from all-cause death, cardiac death and MACE (all death, non-fatal MI and target lesion revascularization/target vessel revascularization (TLR/TVR)) were 87%, 98% and 50%, respectively [20]. The 10 year TLR rate was 28% and there were 2 cases of definite scaffold thromboses in which one was subacute and one was very late (10 years after implant) in which the patient had a sirolimus eluting stent proximal to two Igaki-Tamai stents. Angiographic data from 6 months to 3 years showed an increase in minimum lumen diameter (1.76±0.74 mm to 2.22±0.56 mm) and a decrease in % diameter stenosis (%) (38±22 to 25±18). IVUS evaluation of the target vessel found that after 36 months the Igaki-Tamai stents struts had disappeared and from 6 months to 3 years the minimum lumen area (3.64±1.68 mm^2 to 5.18±2.09 mm^2) and the vessel area (external elastic membrane) increased. The balloon-expandable (i.e., heating not required) Igaki-Tamai

peripheral stent was evaluated in the PERSEUS clinical trial [21], of which results supported approval for CE mark (November 29, 2007).

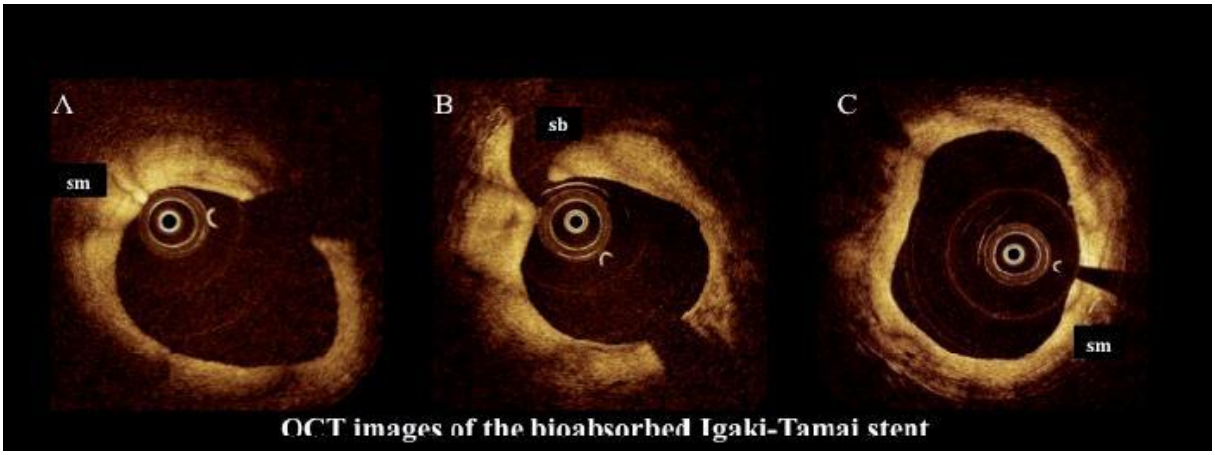


Figure 2.3: OCT Images of Igaki-Tamai Stent at 9 Years

A: Proximal marker; C: Distal marker; B: Bifurcation
The lumen was smooth and strut footprints were not observed.

2.1.9 ABSORB TRIALS

ABSORB Cohort A

Since the development of the drug-eluting stent, there have been significant improvements in PCI clinical outcomes [22-27]. The next endeavor into PCI is the use of polymeric scaffolds, such as the Absorb BVS System. Early evidence with the first iteration of the Absorb BVS System (Absorb Cohort A BVS System) demonstrates similar performance to that of DES, as well as similar physiological and functional changes to the treated region of the vessel. The First in Man ABSORB Cohort A Trial represents the first clinical evaluation of the safety and performance of the Absorb Cohort A BVS System. The ABSORB Cohort A Trial enrolled 30 subjects from 4 clinical sites (the Netherlands, Poland, Denmark, and New Zealand) from March 7, 2006 to July 18, 2006. Subjects with visually estimated nominal vessel diameters of 3.0 mm and lesion(s) length ≤ 14 mm were enrolled. They received a single 3.0 x 12 mm or 3.0 x 18 mm Absorb Cohort A BVS System. The 6-month angiographic in-device late loss (LL) of the Absorb Cohort A BVS System was 0.43 mm, which was larger than the in-stent LL of the XIENCE V stent in the SPIRIT FIRST trial (0.10 mm), but superior to bare metal stents (0.85 mm). The greater late loss associated with the Absorb Cohort A BVS System device was due to scaffold-area loss, suggesting that the scaffold may have prematurely lost the ability to provide luminal support [28] . Contrarily, neointimal proliferation observed in IVUS was smaller compared to the XIENCE V stent (mean neointimal area of the Absorb Cohort A BVS System: 0.30 ± 0.44 mm^2 vs. XIENCE V: 0.61 ± 0.75 mm^2) [29]. Average lumen area significantly decreased between post-procedure and 6-month time points, while it significantly increased between 6-month and 2-year time points. Vessel area between baseline and the 6-month and 2-year time points remained constant demonstrating the absence of negative remodeling. Vasomotion measurements conducted at 2 years showed preliminary indications of restoration of vessel movement in the

treated segment as well as in the distal and proximal segments [30]. Currently, 5-year follow-up has been completed in the Cohort A and there have been no changes in the endpoint event rates between 6 months and 5 years, in which only one ischemic MACE event (NQMI) was reported in the first 6 months of the trial. No scaffold thromboses have occurred in the Cohort A through 5 years of follow-up.

ABSORB Cohort B

Based upon the safety results of the BVS Cohort A device, Cohort B of the ABSORB trial was initiated on March 19, 2009 to evaluate Absorb BVS System (mfg MTV), and completed enrollment on November 6, 2009 with 101 subjects split into two groups: Group 1, n=45 (imaging follow-up at 180 days and 2 years) and Group 2, n=56 (imaging follow-up at 1 year and 3 years). The BVS Absorb BVS System (mfg MTV), is similar to the Cohort A BVS System that was evaluated in Cohort A, but has undergone modifications to the scaffold design and manufacturing processes to improve its mechanical performance and prolong the duration of effective scaffolding. Cohort B is a prospective, open-labeled, multi-center registry that enrolled subjects with up to two *de novo* native coronary artery lesions in separate epicardial vessels with visually estimated nominal vessel diameters of 3.0 mm and lesion(s) length ≤ 14 mm. All subjects in Cohort B received a single 3.0 x 18 mm BVS Cohort B device per lesion treated. The 6-month angiographic results from Cohort B Group 1 demonstrated a late loss of 0.19 mm which is similar to the 0.10 mm late loss of the 3.0 x 18 mm XIENCE V observed in the SPIRIT FIRST trial and compares favorably with the 0.43 mm late loss from Cohort A. At 180 days, the IVUS results from Cohort B Group 1 showed limited intra-scaffold neo-intimal hyperplasia, the volume obstruction (VO) was 1.2% and the neointimal hyperplasia (NIH) area was 0.08 mm^2. These results compare favorably with XIENCE V in SPIRIT FIRST (VO of 8.0% and NIH area of 0.56 mm^2) and with Cohort A (VO of 5.3% and NIH area of 0.29 mm^2). As observed in Cohort A, the 6-month IVUS results showed a significant reduction in the average lumen area (6.60 ± 1.22 mm^2 after procedure vs. 6.37 ± 1.12 mm^2 at 180-day, p=0.0048). This was much lower than that found for the Cohort A BVS System (6.08± 1.13 mm^2 after procedure vs. 5.07± 1.22 mm^2, p=0.0001, at 180-day). The vessel area remained comparable between baseline and 180-day follow-up (14.22 ± 3.75 mm^2 vs. 14.49 ± 3.67 mm^2) demonstrating the absence of negative remodeling.

QCA and IVUS results from baseline, post procedure and 2 year are available for the patients in Cohort B Group 1. The 2-year angiographic results from Cohort B Group 1 demonstrated a late loss of 0.27 mm which compares well to the SPIRIT II XIENCE V 2 year late loss of 0.33 mm. Furthermore, in Cohort B Group 1 (n=33) IVUS data demonstrated lumen, scaffold and vessel enlargement between 6 months and 2 years (**Table 2.3).**

Table 2.3: ABSORB Cohort B Group 1: IVUS Results through 2 Years

	Post-procedure	6 Months	2 years	p-value post vs. 2 years	p-value 6 m vs. 2 years
Average vessel area (mm^2)	14.04 ± 3.80	14.44 ± 3.82	15.35 ± 4.05	< 0.0001	< 0.0001
Average scaffold area (mm^2)	6.53 ± 1.23 (33)	6.42 ± 1.17	7.08 ± 1.73	0.0035	< 0.0001
Average lumen area	6.53 ± 1.24	6.36 ± 1.18	6.85 ± 1.78	0.3515	0.0105

Based on paired analysis. P-values from Wilcoxon signed rank test.

Table 2.4 shows clinical outcomes through 2 years for all subjects (n=100)[19] in the ABSORB Cohort B Trial. There have been no cardiac deaths through 1 year and the MI rate has remained low at 3% from 180 days to 2 years, in which all were non-Q wave MIs. There have been 6 TLRs, resulting in an overall 2-year MACE rate of 9%. As of 2 years no scaffold thromboses have been reported.

Table 2.4: ABSORB Cohort B clinical endpoint event rates through 2 Years

	30 Days	6 Months	12 Months	24 Months
	N=101	N=101	N=101	N=100
Cardiac Death %	0	0	0	0
Myocardial Infarction % (n)	2.0(2)	3.0(3)	3.0(3)	3.0(3)
Q-wave MI	0	0	0	0
Non Q-wave MI (n)	2.0(2)	3.0(3)	3.0(3)	3.0(3)
Ischemia driven TLR %	0	2.0(2)	4.0(4)	6.0(6)
CABG	0	0	0	0
PCI (n)	0	2.0(2)	4.0(4)	6.0(6)
Hierarchical MACE % (n)	2.0 (2)	5.0 (5)	6.9 (7)	9.0 (9)
MACE: Cardiac death, MI, ischemia-driven TLR TVF: Cardiac death, MI, ischemia-driven TLR, ischemia-driven TVR MI per protocol definition used in SPIRIT III and SPIRIT IV				

Three year results for ABSORB Cohort B Group 1 (N=44) have been presented at TCT 2012.[20] At 3 years, the MACE rate was 6.8%, the MI rate was 2.3%, and the ID-TLR rate was 4.5%; all of these were unchanged from 2 years, reflecting that there were no new MACE in this population between 1 year and 3 years. In addition, there were no scaffold thrombosis events by ARC or protocol definitions, and there were no cardiac death. There was one new non-TLR TVR between 2 and 3 years that contributed to a 3 year hierarchical TVF rate of 9.1%.

Vasomotion measurements conducted at 1 year (Cohort B Group 2, N = 32) and at 2 years (Cohort B Group 1, N = 33) showed preliminary indications of restoration of vessel movement in the treated segment.[21]

ABSORB EXTEND

ABSORB EXTEND is an open label, single-arm, continuous access trial targeted to enroll approximately 1000 patients in up to 100 worldwide sites across Europe, Asia-Pacific, Latin America, and Canada. This is a safety and performance trial aimed at enrolling a large clinical cohort with some exclusion criteria, and with minimal interventional imaging follow-up except for an approximate 50 subject OCT subset involving only planned overlapping cases. In addition there is a subset of 100 patients with noninvasive MSCT imaging. ABSORB EXTEND is the first of the ABSORB trials to allow planned overlapping of two Absorb BVS System (mfg MTV). Subjects registered can be treated with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels; the target lesion length must be ≤ 28 mm and

[19] One subject did not complete the 2 year follow-up.
[20] Smits, P. et. al. ABSORB Cohort B Trial: Evaluation of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold (Absorb BVS) in the treatment of patients with de novo native coronary artery lesions, in TCT 2012. 2012 (presentation): Miami, FL.
[21] 1 year vasomotion data from Serruys P.W ACC 2011 oral presentation and 2 year vasomotion data from Ormiston and Serruys TCT 2011 poster presentation

reference vessel sizes must be suitable to be treated with an Absorb BVS System (mfg MTV). The device sizes used thus far in the study that have generated data summarized here have been the 3.0 x 18 mm, 3.0 x 28 mm and 2.5 x 18 mm scaffolds.

Clinical follow-up will be conducted on all subjects registered in the trial for up to 3 years. Interim data snapshot with the cutoff date of 11-January-2012 (n=469)[22] and 18-September-2012 (6 month data n=500 and 1 year data n=250)[23]. Data out to 30 days were available for 451 subjects in ABSORB EXTEND as of 11-January-2012. The MACE rate for ABSORB EXTEND through 11-January-2012 was 2.2% (10/451) out to 30 days, which was driven by MI. The hierarchical and non-hierarchical MI rates were the same at 30 days; both were 2.2% (10/451). There were no cardiac deaths through 30 days and the ID-TLR rate during the 30-day period was 0.2% (1/451). The scaffold thrombosis rate out to 30 days, as defined using the ARC definition in which the subacute (1-30 days) and acute/subacute (0-30 days) rates were both 0.4% (2/451) according to the definite + probable ARC definitions. Data out to 6-months were available for 269 subjects in ABSORB EXTEND as of 11-January-2012. The MACE rate was 3.0% (8/269) [1 cardiac death and 7 MI] at 6 months. The one cardiac death was with a subject that did not receive an Absorb BVS. The 6 month ID-TLR rate was 0.4% (1/269) and the overall (0-194 days) scaffold thrombosis rate was 0.7% (2/268) according to the definite + probable ARC definitions. Data out to 1 year was available for 120 subjects in ABSORB EXTEND as of 11-January-2012. The MACE rate was 5.0% (6/120) [1 cardiac death, 4 MI, and 1 ID-TLR] at 1 year. The overall (0-393 days) scaffold thrombosis rate was 0.8% (1/119) according to the definite + probable ARC definitions.

Six month follow-up data were available for 500 subjects and 1 year follow-up data were available for 250 subjects through 18-September-2012. The MACE rate was 3.0% (15/500) at 6 months and 4.4% (11/250) at 1 year. The overall MI rate was 2.8% (14/500) at 6 months and 2.8% (7/250) at 1 year. The cardiac death rate was 0.2% (1/500) at 6 months and 0.4% (1/250) at 1 year, this cardiac death included the subject that did not receive the Absorb BVS. The 6 month ID-TLR rate was 0.6% due to the occurrence of three ID-TLR events and the 1 year ID-TLR rate was 2.0% due to the occurrence of 5 ID-TLR events. The overall 6 month scaffold thrombosis rate was 0.6%, and the overall 1 year scaffold thrombosis rate was 0.8% according to the definite + probable ARC definitions.

ABSORB II

ABSORB II is a post-approval RCT occurring outside the United States (OUS) that will be the first comparison of the Absorb BVS System against an active control of a metallic DES (XIENCE PRIME). The ABSORB II trial is the first to have powered, co-primary endpoints evaluating both the morphological and functional responses at 2 or 3 years when the device has resorbed (depending on the results of the ABSORB Cohort B trial 3-year imaging follow-up data). The ABSORB II RCT will enroll approximately 501 subjects at approximately 40 investigational sites OUS.

[22] ABSORB EXTEND Annual Progress Report, report dated March 14, 2012.
[23] Bartorelli, A. L. et. al., ABSORB EXTEND: An interim report on the 6 month clinical outcomes from the first 500 patients registered, in TCT 2012. 2012, (presentation): Miami, FL; Bartorelli, A. L. et. al., *ABSORB EXTEND: An interim report on the 12 month clinical outcomes from the first 250 patients registered,* in *TCT 2012.* 2012, (presentation): Miami, FL.

ABSORB PHYSIOLOGY

The ABSORB PHYSIOLOGY trial will evaluate one of the key potential benefits of the Absorb BVS System, which is coronary vessel functionality after bioresorption. The trial will be dedicated to comparing the vascular responses of Absorb BVS treated vessel segments versus metallic DES (XIENCE V or XIENCE PRIME) treated segments, to measure how the vessel accommodates changes in blood flow following physiological stimuli.

2.1.10 SPIRIT TRIALS

The SPIRIT Family of trials is composed of SPIRIT FIRST, SPIRIT II, SPIRIT III, SPIRIT IV and SPIRIT Small Vessel, all of which demonstrated the safety and effectiveness of XIENCE V, which uses the same drug (Everolimus) and has the same drug density (100 µg/cm2) and release profile (80%/28 days) as the Absorb BVS.

The pivotal SPIRIT III trial, which supported the US approval of XIENCE V, was a 2:1 RCT with the primary endpoint of in-segment LL at 240 days. XIENCE V was found to be non-inferior ($p<0.0001$) and superior ($p=0.0037$) to TAXUS in this primary endpoint, with values of 0.14±0.41 (301) and 0.28±0.48 (134), respectively. The 1-year MACE rates were 6.0% (39/655) and 10.3% (33/319) for the XIENCE V arm and TAXUS arm, respectively, and the stent thrombosis rates (definite/probable per ARC) were 1.1% for XIENCE V and 0.6% TAXUS (p=NS). The SPIRIT III RCT has continued to demonstrate safety and efficacy of XIENCE V through 5 years.

The SPIRIT IV clinical trial was a 2:1 randomized clinical trial against TAXUS designed to continue to evaluate the safety and efficacy of the XIENCE V. At 1 year, the XIENCE V arm demonstrated non-inferiority and superiority to the TAXUS arm in terms of TLF (4.2% and 6.8%, respectively, $P_{NI} < 0.0001$, $P_{SUP} = 0.0012$), and the stent thrombosis rates per ARC (definite/probable) were lower in the XIENCE V arm (0.3%) compared to the TAXUS arm (1.1%; p=0.04). SPIRIT IV continues to demonstrate the safety and efficacy of XIENCE V through 3 years.

The SPIRIT PRIME trial, which supports the US approval of XIENCE PRIME, was a prospective, open-label, non-randomized study consisting of two registries with approximately 500 subjects at up to 75 global sites: the Core Size Registry (stent diameters 2.25. 2.5, 3.0, 3.5, 4.0 mm with stent length 8, 18, and 28 mm) and the Long Lesion Registry (stent diameters 2.5, 3.0, 3.5, 4.0 mm with stent lengths 33 and 38 mm). Each subject was to receive treatment in up to two *de novo* native coronary lesions, each lesion in a different epicardial vessel. SPIRIT PRIME Core Size and Long Lesion Registries met all pre-specified PGs with statistical significance. The observed TLF rate at one year was 4.5% (18/399) (per protocol-defined MI) and 6.5% (26/399) (per ARC-defined MI) in the Core Size Registry, and 7.7% (8/104) (per protocol-defined MI) and 12.5% (13/104) (per ARC-defined MI) in the Long Lesion Registry, respectively.

Further details on the SPIRIT Family of trials can be found in the XIENCE V IFU and XIENCE PRIME IFU.

2.1.11 Patient Reported Outcomes (PRO)

In clinical trials, patient reported outcome instruments can be used to measure the impact of an intervention on several aspects of patient health status and quality of life. Since improvements in clinical measures may not necessarily correlate with how the patient feels or functions, understanding the patient perspective on treatment effectiveness can be extremely valuable. Obtaining the patient's perspective may also provide additional information that may not be fully captured through clinician-centered evaluations.

In addition, as health expenditures have continued to rise, it is no longer sufficient for new therapies to simply demonstrate efficacy in order to be accepted into mainstream medical practice. Today, physicians, payers, and policy-makers have become increasingly interested in understanding the overall value of therapies. Patients' self-reported health-related quality of life outcomes help to determine the full impact of treatment benefit and serve as key inputs when assessing the value of this impact.

Patient Reported Outcome instruments will be incorporated in the 2,000 primary analysis subjects in ABSORB III to provide a complementary evaluation of the effectiveness of the Absorb BVS system. The following instruments will be administered during this study at pre-implantation, 30 days, 1, 2, 3 and 5 years follow-up:

- EuroQoL 5D (EQ-5D) survey to assess overall health status
- Seattle Angina Questionnaire (SAQ) to assess disease-specific QoL
- Rose Dyspnea Scale (RDS) to assess severity of dyspnea*
- Generalized Anxiety Disorder scale (GAD-7) to assess anxiety*

*RDS and GAD-7 will only be used through 3 years.

2.2 Trial Rationale

As mentioned in **Section 2.1.9,** the Absorb BVS System is being evaluated in ABSORB Cohort B and ABSORB EXTEND, all single arm, non-randomized clinical trials. Currently, only retrospective descriptive comparisons provide insight into the performance of the Absorb BVS System (mfg MTV) compared to XIENCE V. In the Cohort B trial, Absorb BVS System (mfg MTV) showed a similar 1-year (BVS 0.27 mm and XIENCE V 0.23 mm) and 2-year LL measurement (BVS 0.27 mm and XIENCE V 0.33 mm) compared to XIENCE V and the 1- year (6.9%), 2-year (8.9%) and 3-year (8.9%) MACE rates (Kaplan Meier estimate) for Absorb BVS System (mfg MTV) were comparable to the 3.0 x18 mm XIENCE V 1-year (7.5%), 2-year (8.5%) and 3-year (11.4%) MACE rates (Kaplan Meier estimate) from pooled SPIRIT data (SPIRIT FIRST, SPIRIT II and SPIRIT III RCT). ABSORB III provides the first robust head-to-head comparisons of the Absorb BVS to XIENCE, and is designed to demonstrate non-inferiority for the 1-year clinical endpoint of TLF with Absorb BVS compared to XIENCE. Furthermore, ABSORB III will provide the opportunity to evaluate the long term benefits of Absorb BVS compared to XIENCE in regards to potential functional as well as dynamic (i.e., vessel movement) and morphological (i.e., late lumen enlargement) changes to the treated vessel.

3. TRIAL OBJECTIVE

ABSORB III Primary Objective: The pivotal trial to support the US pre-market approval (PMA) of Absorb BVS. ABSORB III will evaluate the safety and effectiveness of the Absorb BVS System compared to the XIENCE in the treatment of subjects, including those with diabetes mellitus, with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels.

ABSORB III Secondary Objectives:

- **Lead-In Phase Objective:** To evaluate the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice.

- **Imaging Cohort Objective:** To evaluate long-term vascular function and patency of the Absorb BVS treated segments compared to XIENCE treated segments in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels.

4. CLINICAL TRIAL/INVESTIGATION FLOW AND FOLLOW-UP SCHEDULE

4.1 Number of Subjects to be Registered

Approximately 2250 subjects will be registered in ABSORB III. Of this total number, up to 50 subjects will be registered in the Lead-In phase, 2000 subjects will support the primary endpoint analysis and 200 subjects will be registered in the Imaging Cohort.

4.2 ABSORB Physician Training

The ABSORB III training program is a two-phased approach that will combine 1) didactic learning and 2) vessel sizing test-runs with corresponding retrospective core laboratory analysis.

All investigators (primary investigators and sub-investigators) will be required to undergo didactic training. The didactic learning will involve both self-learning of provided materials, meeting-based peer to peer learning or site learning conducted by Abbott Vascular trained staff. The investigators will receive an Absorb BVS training package that will include the training on the following elements: 1) technology overview, which includes the rationale and goals for a bioresorbable scaffold and the description of the Absorb BVS, with specifics on the polymer, delivery system and the three phases of functionality (revascularization, resorption and restoration) associated with Absorb BVS. 2) Update on the most current ABSORB program pre-clinical and clinical data. 3) Patient and lesion selection which includes the indication, contraindications and warnings for the use of Absorb BVS. There will also be a review of the general and angiographic inclusion and exclusion criteria, with emphasis on the avoidance of specific lesion criteria that could result in adverse outcomes. 4) Lesion preparation and treatment strategy, which will detail the ABSORB III protocol-required criteria on the appropriate preparation of the potential target lesion and sizing of the vessel prior treatment. 5) Case reviews specific to lessons learned from the previous ABSORB trials. 6) Device usage and logistics which includes details on device storage, sheath removal and general instructions for

use. The section will also include information on packaging, product handling, storage and shelf-life and device accountability.

The ABSORB III site primary investigators and sub-investigators attending the investigator meeting will receive peer-to-peer learning which will include, an update on the most recent Absorb BVS clinical and pre-clinical data and current clinical practice, Absorb BVS characteristics and differences compared to metallic DES, patient and lesion selection, appropriate techniques to size the vessel, practical recommendations on how to implant Absorb BVS and the indications for Absorb BVS based on ABSORB III. There will also be case review discussions by physicians that have treatment experience with Absorb BVS and the dos and don'ts of treatment. The ABSORB III didactic learning phase was developed from the learning and strategies used in the ABSORB Cohort B, ABSORB EXTEND and ABSORB II trials.

At the investigator meeting, the didactic training will also include hands-on training through the use of simulated arterial models (SAM), in which there will be learning on the device handling outside of and within the model coronary vasculature. The SAM training will be conducted by Abbott Vascular employees well trained in the handling and delivery of the Absorb BVS. The physicians will be educated on the scaffold, the delivery system, the scaffold profile differences as compared to XIENCE, and direction on the removal of the Absorb BVS' protective sheath. Physicians will have an opportunity to undergo exercises that will allow them to experience the differences in the delivery and deployment between XIENCE and Absorb BVS in an in vitro model. Discussions will be held regarding proper lesion preparation and specific techniques that have been used by physicians with prior experience implanting Absorb BVS in patients. In the SAM training, physicians will also be able to undergo exercises to understand the expansion capabilities of the Absorb BVS.

For those investigators not attending the investigator meeting, Abbott Vascular (AV) staff trained on the use of Absorb BVS will provide detailed training at site initiations. The training will include the topics mentioned above, including but not be limited to, the investigational plan, investigational device usage, clinical investigation plan requirements, electronic case report form completion, and clinical investigation personnel responsibilities. Specific to the device usage, the clinical research associate (CRA) will train the investigators on appropriate use of the device, including (but not limited to) reintroduction of the device, dwell time in the body, use of adjunctive devices, removal of the device and expansion/post dilatation guidelines.

All investigator/clinical investigation personnel that are trained must sign a training log. No investigator/clinical investigation personnel will perform any clinical investigation-related procedures prior to signing a training log. Furthermore, the site primary investigator (or designee) that attended the investigator meeting will be asked to serve as the site physician expert to provide feedback to his/her sub-investigators on their experience with the hands-on training with Absorb BVS and any further learning. However, if investigators at the site need further training regarding Absorb BVS, AV will provide this service.

Prior to enrollment in ABSORB III, two angiographic test runs that provide a visual estimation of RVD on non-study PCI patients must be completed by the Investigators. Visual RVD estimates can be sent to the Angiographic Core Laboratory for review to correlate the investigator's visual estimation of RVD with quantitative angiographic readings by the Core Laboratory. The test runs can be performed prior to the clinical sites trial start-up or using retrospective PCI cases in which the non-study patient has given consent for the data to be used.

Investigators will be required to complete a minimum of two visually estimated cases and both must meet the specified sizing requirements as assessed by the core laboratory. If an investigator has participated in AV coronary trials, visually estimated RVD data and the corresponding core laboratory assessment can also be used for the test run. All test run data must have been completed no earlier than June 2009. Complete details on the test-runs can be found in the physician training slides and the imaging guidance document that will be distributed to each site.

Supplemental quantitative information from on-line quantitative angiography, intravascular ultrasound, or optical coherence tomography can be used to confirm measurements of the vessel, if the clinical site chooses. Please review the Imaging Guidance Document for further details.

4.3 Lead-In Phase

ABSORB III will include a Lead-In Phase that will provide an opportunity to evaluate whether the Absorb physician training, developed from the ABSORB programs outside the US, can be applied to US clinical practice.

The Lead-In Phase will enroll/register subjects prior to the randomization of the 2000 subjects supporting the primary analysis. The objective of the Lead-In Phase will be the evaluation of the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice. The primary area of learning in the usage of Absorb BVS includes the vessel sizing, lesion preparation, device delivery and deployment, as these variables reflect the change in practice that occurs with the use of a polymeric scaffold compared to a metallic stent. The Lead-In Phase will involve up to 35 US sites and up to 50 subjects treated with Absorb BVS.

There will be four key areas of evaluation of the Lead-In Phase, 1) angiographic inclusion/exclusion, 2) vessel sizing meeting protocol required criteria, 3) treatment strategy per protocol requirements and 4) device success. Each of these variables will provide a measure of adherence to the physician training program. The data for each registered subject will be collected through the electronic case report forms (eCRFs). The outcomes will determine whether the physician training requires further modification to meet the needs of the US physicians. Details on how the sponsor will evaluate the Lead-In Phase can be found in Appendix VII.

The first Absorb BVS case for each investigator participating in the Lead-In will be attended by an Abbott Vascular (AV) CRA. The objective of the CRA-attended cases is to provide an opportunity for the investigator to receive guidance on and reinforcement of the Absorb BVS teachings (detailed in **Section 4.2**) during their Absorb BVS enrollment. The CRA field group will be trained on Device Handling Fundamentals and all elements of the protocol. At the time of the procedure, the CRA attendant will be available to provide review of the key protocol requirements and device usage elements prior to the start or during the index procedure. The sponsor CRA will make every attempt to ensure that the first Absorb BVS case is attended in person. However, a diagnostic angiogram is often not performed on a separate date prior to PCI for pre-screening. In these instances, since the diagnostic catheterization (qualifying cardiac catheterization) and the intervention are done at the same setting (with limited amount of time in-between), AV would be unable to travel to the site and attend in person. For these sites, AV personnel will be available to provide telephone guidance and reinforcement prior to the start of the index procedure.

Prior to the index procedure, the CRA will review the 4 variables with the enrolling physician: 1) angiographic inclusion/exclusion criteria requirements; 2) vessel treatment strategy; 3) appropriate vessel sizing and scaffold selection; and 4) appropriate device preparation and usage. If the CRA is at the site in person, once this information is reviewed and the index procedure has occurred, the CRA will complete the Lead-In checklist for the investigator and submit this information to AV for filing. If the CRA is not present, the site will be requested to complete the eCRF within 1-2 business days of the procedure, which will be remotely monitored by the CRA within 1-2 business days of data entry. If the CRA is present at the time of the index procedure, the site will have 2 business days to enter the subject data into the eCRF.

In addition to the CRA guidance provided onsite or via telephone, during the site initiation visit, the site will be provided with a similar checklist and reference tools in order to ensure that they have the necessary information readily available to ensure appropriate subject selection, vessel treatment strategy, vessel sizing and Absorb BVS selection as well as appropriate device preparation and usage.

Angiograms should be submitted to the core laboratory within 2 business days following the procedure for analysis to ensure appropriate vessel sizing and scaffold usage (for details on imaging uploading refer to **Imaging Guidance Document**). This feedback will be provided to the site within 72 hours of submitting the angiogram. If discrepancies are identified by the angiographic core laboratory specific to vessel sizing and the %DS required for analyzing device success (< 30%), the angiographic core laboratory and the CRA, respectively, will contact the investigator to discuss the issue and any corrective measures necessary to avoid the issue in future cases. Investigators not meeting all four criteria (CRA assessed and core laboratory assessed), will be retrained on the missed elements by the AV CRAs and/or core laboratory if necessary prior to their next Absorb BVS case. Depending on the elements missed, the CRA may attend the next Absorb BVS case to ensure criteria are met. At any time during the Lead-In phase, if AV or the site determines that further site/investigator training is required, such training will be arranged.

4.4 ABSORB III Treatment Flow and Lesion Selection

The same treatment flow and lesion selection applies to all subjects in ABSORB III (including the Lead-In Phase and the Imaging Cohort). Either one or two target lesions in two separate epicardial vessels will be treated. If only one target lesion is intended, a second non-target lesion in a different epicardial coronary artery than the target lesion may also be treated prior to the target lesion. For the Lead-In Phase, only Absorb BVS will be used for target lesion (s).

Figure 4.1 shows the lesion treatment for subjects in the Lead-In Phase.

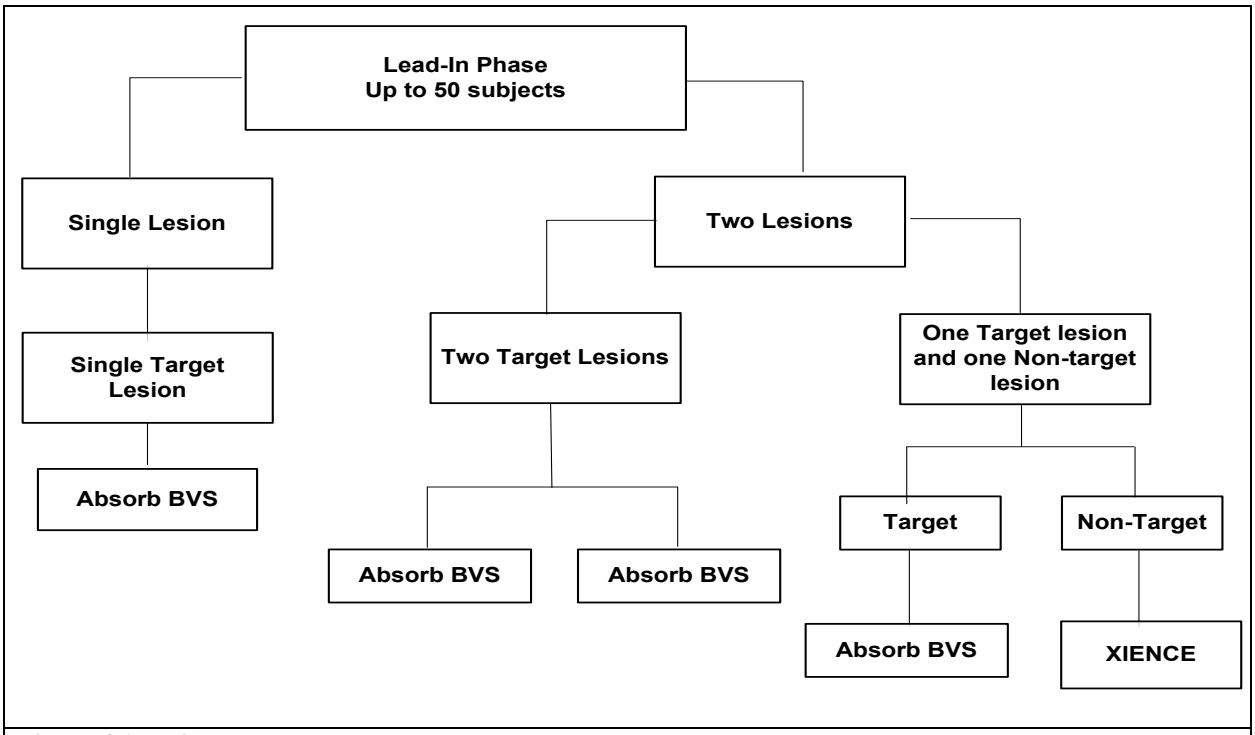


Figure 4.1 Lesion Treatment

Figure 4.2 shows the lesion treatment for the 2200 randomized subjects.

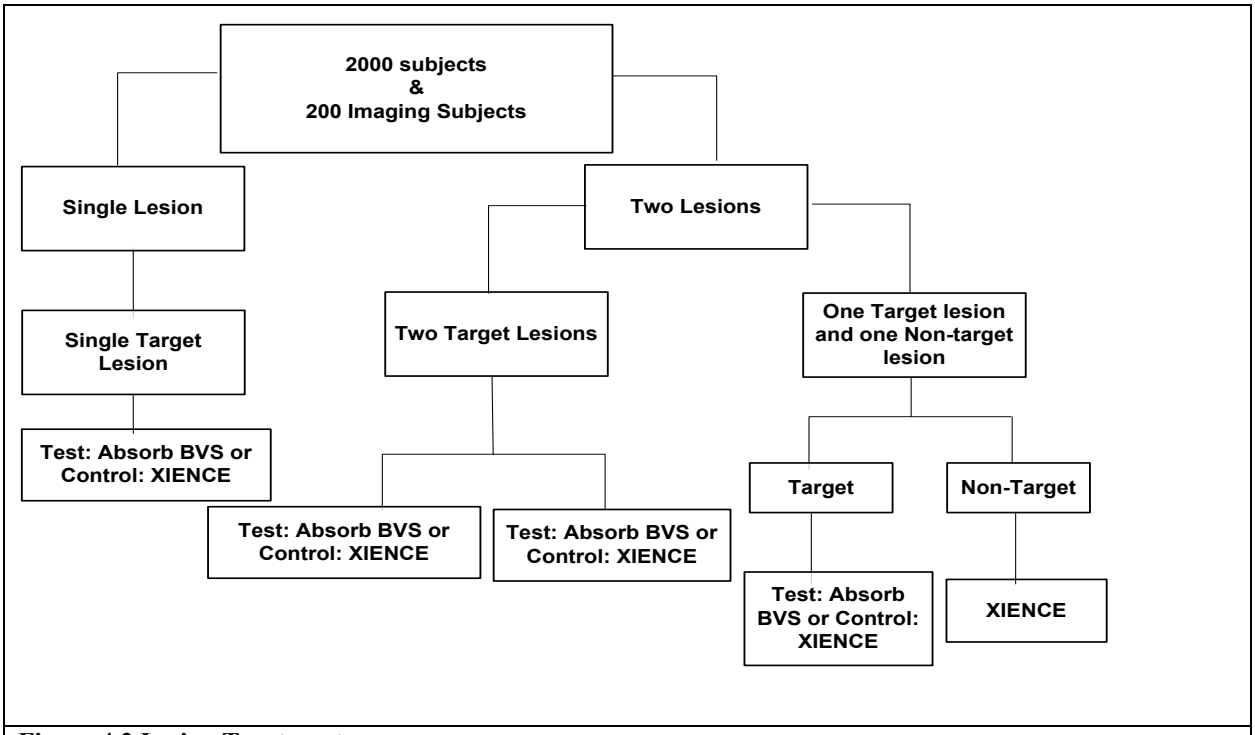


Figure 4.2 Lesion Treatment

If a non-target lesion is present, the non-target lesion must be successfully treated first with a XIENCE stent. Despite the allowance of two lesion treatment, planned staged procedures are not allowed in ABSORB III.

Prior to treatment with the assigned device (Absorb BVS or XIENCE), vessel sizing by visual estimation must be conducted to appropriately match the device to the size of the vessel. Quantitative methods such as on-line QCA, IVUS or OCT may be used if deemed necessary per physician discretion, but are not required. Details on the vessel sizing methods can be found in **Imaging Guidance Document (**detailed in **Section 7.3.2)**.

Table 4.1 provides the device sizes, RVD and lesion length for ABSORB III.

Table 4.1 Absorb BVS and XIENCE Sizes

	Lesion and Device Sizes	
Device	RVD [1]	Lesion Length[1]
Lead-In Absorb BVS (Target lesion)	RVD ≥ 2.75 mm - ≤ 3.25 mm Scaffold diameter: 3.0 mm	Lesion length ≥ 8-≤ 14 mm Scaffold length: 18 mm
RCT Absorb BVS (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Scaffold diameter: 2.5, 3.0 and 3.5 mm	Lesion length ≤ 24 mm Scaffold Length[2]: 8, 12, 18 and 28 mm [3]
RCT XIENCE[5] (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Stent diameter: 2.5, 2.75, 3.0, 3.25, 3.5, 4.0 mm	Lesion length ≤ 24 mm Stent Length: 8, 12, 15, 18, 23 and 28 mm [3]
XIENCE (Non-target lesion)	Per IFU (RVD ≥ 2.25 mm - ≤ 4.25 mm can be treated) All available sizes	Per IFU (lesion ≤ 32 mm) [4] All available sizes

[1] Reference vessel diameter (RVD) and lesion length based on visual estimation
[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23 mm Absorb BVS device will not be used in this study.
[3] For target lesion, planned overlapping is not allowed (i.e., the lesion must be eligible for treatment with a single stent). However, bailout overlapping is allowed if required.
[4] For non-target lesion, planned overlapping allowed.
[5] XIENCE V, XIENCE Prime, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^X are used in this study.

The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.

A minimum of 2 mm (by visual estimation) of minimally diseased tissue should be covered by the device at both the proximal and distal edges.

Planned overlap of the target lesion is not allowed. Overlap in the case of bailout is allowed for both the target and non-target lesion. Please refer to **Section 7.3.5** for details regarding bailout.

4.5 Measures Taken to Avoid and Minimize Bias

In ABSORB III there will be several measures taken to avoid and minimize bias such as randomization and blinding. This process has been detailed in the following sections.

4.5.1 Randomization

Stratified Randomization:

Approximately 2000 subjects will be randomized 2:1 in the primary analysis (test device: Absorb BVS vs. control device: XIENCE). As diabetes and dual lesion treatment are known risks that may influence the rate of the composite endpoint (TLF), subjects will be stratified by diabetes mellitus (diabetic vs. non-diabetic) and dual vessel treatment (single target lesion vs. dual target lesion vs. one target lesion and one non-target lesion). Subjects will also be stratified by site at some pre-specified sites (expected high-enrolling sites). Other sites will be combined to ensure a sufficient number of subjects for the attainment of the desired randomization ratio. In the Imaging Cohort for both subjects receiving IVUS and those receiving the OCT, randomization (2:1) will be stratified by diabetes mellitus (diabetic vs. non-diabetic) and intended dual vessel treatment (single target lesion vs. dual target lesion vs. one target lesion and one non-target lesion). A centralized randomization service, IVRS, will be used.

Timing of Randomization:

Randomization will be done after successful treatment of the non-target lesion (if any) and successful and uncomplicated pre-dilatation of the target lesion (or the first target lesion if there are two target lesions) and vessel sizing (refer to **Section 7.3.4**, Treatment Rules of the Target Lesion, for details). Once randomization is completed and a treatment is assigned, crossover is not permitted. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment. An Absorb BVS scaffold may never be used in a patient randomized to XIENCE. However, if the patient is randomized to Absorb BVS and the scaffold cannot be delivered or a complication otherwise develops that requires treatment with a XIENCE stent, a XIENCE or any other stent may be used as necessary in the best interests of the patient.

The subject is considered to be successfully registered in this study and considered in the ITT population at the point of randomization (refer to Section 6.4). Lead-In subjects will be considered registered in the study upon calling IVRS. Refer to Appendix IV (Figure 1 and 2) for enrollment and registration timeline and flow chart.

4.5.2 Blinding

This is a single-blinded clinical trial. Subjects will be blinded to their treatment assignment and the study site personnel will be trained not to disclose the treatment assignment to the subject. Additionally, blinded site personnel, not present at the index procedure, will be assigned to conduct the clinical follow-up and they will be provided with a standard follow-up interview script in order to reduce bias and maintain subject blinding. Subject blinding should be maintained until the 5-year follow-up visit for all subjects is completed.

The physician performing the procedure will not be blinded to the assigned treatment. Thus, if a clinical follow-up with a study physician is deemed necessary at the protocol required follow-up time points, a different physician (or designee) than the one who implanted the device(s) should conduct follow-up clinical visits in order to maintain subject blinding. However for the Imaging Cohort, the protocol-required imaging follow up can be done by the same physician who implanted the device. Site personnel will be adequately trained such that the physician (or

designee) conducting the clinical follow-up is adequately blinded to the treatment received by the subject. For unscheduled visits, subjects may see the physician who implanted the device(s). Treating physicians should conduct all non-protocol related visits with the subject with caution, to prevent unblinding of the subject.

The Clinical Events Committee (CEC) will be blinded to the randomization assignments. The angiographic, IVUS and OCT core laboratories cannot be blinded to the device received. The Data Safety Monitoring Board (DSMB) will also be blinded to the subject's randomization. Independent statisticians will generate blinded tables for review by the DSMB. The DSMB may request unblinded data if a safety signal is observed.

Sponsor personnel that will be unblinded will be the independent biostatisticians involved in generating and verifying the randomization code, key Clinical Science and Operations, Clinical Safety Monitor, Site Monitors, Clinical Data Management, Electronic Database Programmer, Inventory Management staff, and Clinical Information System (IS) personnel working on the trial. Restricted access of blinded personnel to the clinical database will be maintained until unblinding of the study.

4.6 Early Termination of the Clinical Trial

Sponsor reserves the right to discontinue the Clinical Investigation at any stage, with suitable written notice to the investigator. The investigator may also discontinue participation in the Clinical Investigation with suitable written notice to Sponsor. Should either of these events occur, the investigator shall return all documents and devices to the Sponsor, provide a written statement as to why the premature termination has taken place, and notify the Ethics Committee and the regulatory authority (if applicable). All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in the **Section 13.0** Data Handling and Record Keeping.

All subjects registered up to the point of trial discontinuation will continue to be followed up per protocol requirements.

5. ENDPOINTS

5.1 Primary Endpoint

ABSORB III Primary Endpoint

1. TLF at 1 year, non-inferiority (NI) against the control.

   - TLF is defined as composite of Cardiac Death, Myocardial Infarction (per protocol-defined MI definition, Appendix II) attributable to Target Vessel (TV-MI), or Ischemia-Driven Target Lesion Revascularization (ID-TLR).

   - This analysis will include ~2000 subjects.

5.2 Powered Secondary Endpoint(s)

Imaging Cohort Powered Secondary Endpoints

Imaging Cohort Powered Secondary Endpoints are based on the pooled subjects from the Imaging Cohort of Absorb III (~ 200 angiographic subjects and ~150 IVUS subjects) and subjects from the Absorb Japan RCT (~ 400 angiographic subjects, and ~150 IVUS subjects).

One of the key attributes that differentiates Absorb BVS from metallic stents is the progressive mechanical weakening of the scaffold with polymer degradation over time, which allowed for vessel movement and gradual outward remodeling (positive) to accommodate any increases in the in-scaffold intimal hyperplasia that may limit blood flow. In both the Absorb Cohort A and Cohort B trials, Absorb BVS treated vessels have shown evidence of vessel movement and late lumen and scaffold enlargement, providing anatomic indication that the vessel can adapt and enable the natural Glagov process.[24]

The vasomotion endpoint assesses the ability of the in-scaffold segment to move when the vessel is no longer mechanically constrained. Angiography will be used for the vasomotion assessment. The assessment of late lumen enlargement will be evaluated by the in-stent/scaffold mean lumen area change (ΔMLA) from post-procedure to 3 years by IVUS.

1. The in-stent/scaffold mean lumen area change, from post-procedure to 3 years by IVUS (mean lumen area measured after nitrate infusions, superiority test, ~300 pooled subjects).

2. The in-stent/scaffold mean lumen diameter change, between pre- and post-nitrate infusion at 3 years by angiography (superiority test, ~600 pooled subjects).

Powered Secondary Endpoint for Angina

This powered secondary endpoint is intended to assess angina at 1 year and test for superiority of Absorb BVS to XIENCE.

- Angina is defined as the first adverse event resulting in the site diagnosis of angina.

- The analysis will exclude angina following the index procedure through discharge, not to exceed a period of 7 days.

This analysis will include ~2000 subjects.

Powered Secondary Endpoint for All Revascularization

This powered secondary endpoint is intended to assess all revascularization at 1 year and test for superiority of Absorb BVS to XIENCE.

This analysis will include ~2000 subjects.

Powered Secondary Endpoint for Ischemia-Driven Target Vessel Revascularization

This powered secondary endpoint is intended to assess ischemia-driven target vessel revascularization at 1 year and test for superiority of Absorb BVS to XIENCE.

[24]Glagov S, Weisenber W, Zarins CK et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987; 316: 1371-1375.

This analysis will include ~ 2000 subjects.

Powered Secondary Endpoint for Diabetic Indication

The powered secondary endpoint will be to support a diabetic indication for Absorb BVS.

5.3 Additional Secondary Endpoint(s)

In ABSORB III the following clinical secondary endpoints will be analyzed. Secondary imaging endpoints will be analyzed in the Imaging Cohort.

- **Acute Success**: (Combined Clinical/Angiographic Endpoint)
  - Device success (Lesion level analysis)
  - Procedural success (Subject level analysis)
- **Clinical Endpoint** in hospital and at each follow-up point (30 days; 180 days; 1, 2, 3, 4 and 5 years).
  - **Component**
    - Death (Cardiac, Vascular, Non-cardiovascular)
    - Myocardial Infarction
      - Attributable to target vessel (TV-MI)
      - Not attributable to target vessel (NTV-MI)
    - Target Lesion Revascularization (TLR)
      - Ischemia driven TLR (ID-TLR)
      - Non ID TLR (NID-TLR)
    - Target Vessel Revascularization (TVR,)
      - ID TVR
      - Non ID TVR
    - All coronary revascularization
  - **Composite Endpoints**
    - Death/All MI
    - Cardiac Death/All MI
    - Cardiac Death/TV-MI/ID-TLR (TLF)

- Cardiac Death/All MI/ID-TLR (MACE)
- Cardiac Death/All MI/ID-TLR/ID-TVR, non TL (Target Vessel Failure, TVF)
- Death/All MI/All revascularization

- **Scaffold-Thrombosis / Stent Thrombosis (per ARC definition)**
  - Timing (acute, sub-acute, late and very late)
  - Evidence (Definite and Probable)

- **Imaging Endpoints:**

Imaging endpoints will be analyzed on Imaging Cohort subjects only.

- **Angiography:**

All angiographic endpoints will be collected post-procedure and at 3 years

- In-segment[25] late loss (LL)
- In-device[26] LL
- Proximal LL (proximal defined as 5 mm of tissue proximal to the device placement)
- Distal LL (distal defined as 5 mm of tissue distal to the device placement)
- In-device/in-segment/proximal/distal minimum lumen diameter
- In-device/in-segment/proximal/distal %Diameter Stenosis (DS)
- In-device/in-segment/proximal/distal angiographic binary restenosis
- In-device net gain (change in minimum lumen diameter between 3 years and post-procedure)
- The magnitude of in-stent/scaffold mean lumen diameter change (absolute value) at 3-years follow-up from pre-nitrate to post-nitrate
- The normalized in-stent/scaffold mean lumen diameter change at 3-years follow-up from pre-nitrate to post-nitrate, defined as,

$$\frac{\text{In - Stent/Scaffold Mean Lumen Diameter change}}{(\text{Proximal Mean Lumen Diameter change} + \text{Distal Mean Lumen Diameter change})/2} \times 100\%$$

[25] In-device refers to the margins of the stent or scaffold. Segment refers to the margins of the stent or scaffold and 5 mm proximal and 5 mm distal to the stent or scaffold.
[26] Device throughout the protocol summary refers to XIENCE or Absorb BVS System

where both proximal and distal mean lumen diameter changes are at 3-years follow-up from pre-nitrate to post-nitrate

- Change in minimum lumen diameter, within treated segment, at 3 years follow-up from pre-nitrate to post-nitrate
- Change in in-device %DS at 3 years follow-up from pre-nitrate to post-nitrate

- **IVUS (Grey scale):**

All IVUS endpoints will be collected post-procedure and at 3 years (as applicable) and within the device and within the treated segment:

- Minimal Lumen Area
- Percentage of subjects with late gain without incomplete apposition by IVUS (IVUS minimum lumen area post- procedure post-nitrate - IVUS minimum lumen area 3 years follow-up post-nitrate)
- % change in the tissue area/volume between lumen and external elastic lamina (EEL)
- Absolute change in tissue area/volume between lumen and EEL
- Mean/minimal vessel diameter/area/volume
- Mean/minimal device diameter/area/volume; if analyzable in respect to Absorb BVS
- Mean/minimal lumen diameter/area/volume, including change in minimum lumen area between post-procedure and follow-up
- Mean/maximal neointima hyperplasia area/volume/percentage at 3 years; if analyzable in respect to Absorb BVS
- Incomplete apposition (post-implantation), persisting incomplete apposition, late acquired incomplete apposition and resolved incomplete apposition at 3 years; if analyzable in respect to Absorb BVS

- **OCT:**

All OCT endpoints will be collected post-procedure and 3 years, and for within the device and within the treated segment:

- Descriptive analysis of strut, lesion and vessel morphology
- Mean neointimal area (NIA)
  - Apposed to the vessel wall with neointimal coverage
  - Apposed to vessel wall without neointimal coverage

- Incomplete apposition to vessel wall with neointimal coverage
- Incomplete apposition to vessel wall without neointimal coverage

- Lumen area/volume stenosis %
- Mean/minimal device area
- Mean/minimal luminal area/volume
- Mean strut area/volume
- Persisting incomplete apposition, late incomplete apposition at 3 years (if analyzable)
- OCT analysis for subjects with jailed side branch
- Descriptive analyses from 3-dimensional OCT reconstructions

5.4 Informational Endpoints (Patient Reported Outcomes)

In the 2000 primary analysis subjects of ABSORB III the following Patient Reported Outcomes will be analyzed as informational endpoints.

- Overall Health Status in hospital (baseline) and at the specified follow-up contacts (30 days; 1, 2, 3 and 5 years) assessed using the EuroQoL 5D (EQ-5D)
- Disease-Specific Quality of Life in hospital (baseline) and at the specified follow-up contacts (30 days; 1, 2, 3 and 5 years) assessed using the Seattle Angina Questionnaire (SAQ)
- Dyspnea severity in hospital (baseline) and at the specified follow-up contacts (30 days; 1, 2 and 3 years) assessed using the Rose Dyspnea Scale (RDS)
- Anxiety in hospital (baseline) and at the specified follow-up contacts (30 days; 1, 2 and 3years) assessed using the Generalized Anxiety Disorder scale (GAD-7)

6. SUBJECT SELECTION AND WITHDRAWAL

6.1 Subject Population

Subjects registered into this Clinical Investigation will be male and female subjects derived from the general interventional cardiology population. The Clinical Investigation will register approximately 2250 subjects, with a maximum of two *de novo* native coronary artery lesions in separate epicardial vessels, who meet all eligibility criteria, have provided written Informed Consent and have been registered in the trial.

6.2 Subject Screening and Informed Consent

6.2.1 Subject Screening

Subjects planned to be admitted for a percutaneous coronary artery revascularization procedure should be screened for Clinical Investigation eligibility by a member of the research team previously trained to the Clinical Investigation Plan.

Subjects that have signed an Informed Consent (Refer to **Appendix IV**, Enrollment and Registration Process) are considered enrolled in ASBORB III. Subjects who do not satisfy the general angiographic inclusion and exclusion criteria and/or have unsuccessful pre-dilatation and/or vessel sizing are considered screen failures and will not proceed further in the trial. These subjects will be entered into the eCRF screening log (as applicable; in addition, the reason for screen failure as well as supporting data will be entered into the log).

6.2.2 Informed Consent

The Investigator or designee, who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the subjects. All subjects (or legally authorized subjects' representatives, if applicable) must sign and date the Institutional Review Board (IRB) /Medical Ethics Committee (MEC) approved informed consent prior to any clinical trial/investigation-specific procedures. No patients belonging to a vulnerable population will be enrolled. Vulnerable population is defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

Obtaining of the consent, provision of a copy to the subject, along with the date must be documented in the subject's medical records. The informed consent form must be signed by an investigator or designate trained on the protocol. In addition, the signed informed consent must be kept in the subject's medical records/research chart and a copy must be given to the subject or the legally authorized representative.

In addition, an authorization for use and disclosure of the subjects' protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally authorized representative (US only).

For Live cases at congresses the patients need to sign a specific Live Case ICF, approved by the IRB/EC and by Abbott Vascular, as well as by the competent authorities (e.g., FDA), as applicable. The investigator must request Abbott Vascular approval prior to, performing a Live Case.

6.3 Eligibility Criteria

Eligibility criteria are the same for all subjects in ABSORB III, unless specified.

6.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on the medical records of the site and interview with a candidate subject. Clinical and laboratory test of the eligibility assessment shall be per site standard of care. If some of these tests are not included in the site's standard tests, they must be done, but after written Informed Consent has been obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical evaluation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical evaluation and cannot be registered.

6.3.1.1 General Inclusion Criteria

1. Subject must be at least 18 years of age.

2. Subject or a legally authorized representative must provide written Informed Consent prior to any study related procedure, per site requirements.

3. Subject must have evidence of myocardial ischemia (e.g., stable, unstable angina, post-infarct angina or silent ischemia) suitable for elective PCI. Subjects with stable angina or silent ischemia and < 70% diameter stenosis must have objectives sign of ischemia as determined by one of the following, echocardiogram, nuclear scan, ambulatory ECG or stress ECG). In the absence of noninvasive ischemia, FFR must be done and indicative of ischemia.

4. Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery.

5. Female subject of childbearing potential who does not plan pregnancy for up to 1 year following the index procedure. For a female subject of childbearing potential a pregnancy test must be performed with negative results known within 7 days prior to the index procedure per site standard.

6. Female subject is not breast-feeding at the time of the screening visit and will not be breast-feeding for up to 1 year following the index procedure.

7. Subject agrees to not participate in any other investigational or invasive clinical study for a period of 1 year following the index procedure.[27]

[27] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

6.3.1.2 General Exclusion Criteria

1. Any surgery requiring general anesthesia or discontinuation of aspirin and/or an ADP antagonist is planned within 12 months after the procedure.

2. Subject has known hypersensitivity or contraindication to device material and its degradants (everolimus, poly (L-lactide), poly (DL-lactide), lactide, lactic acid) and cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated.

3. Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to clopidogrel and prasugrel and ticagrelor; or to heparin and bivalirudin, and therefore cannot be adequately treated with study medications.

4. Subject had an acute myocardial infarction (AMI: STEMI or NSTEMI) within 72 hours of the index procedure and both CK and CK-MB have not returned to within normal limits at the time of index procedure; or subject with stable angina or silent ischemia has CK-MB that is greater than normal limits at the time of the index procedure.

5. Subject is currently experiencing clinical symptoms consistent with new onset AMI (STEMI or NSTEMI), such as nitrate-unresponsive prolonged chest pain with ischemic ECG changes.

6. Subject has a cardiac arrhythmia as identified at the time of screening for which at least one of the following criteria is met:[28]

    a. Subject requires coumadin or any other agent for chronic oral anticoagulation

    b. Subject is likely to become hemodynamically unstable due to their arrhythmia

    c. Subject has poor survival prognosis due to their arrhythmia

7. Subject has a left ventricular ejection fraction (LVEF) < 30% assessed by any quantitative method, including but not limited to echocardiography, MRI, Multiple-Gated Acquisition (MUGA) scan, contrast left ventriculography, PET scan, etc. LVEF may be obtained within 6 months prior to the procedure for subjects with stable CAD. For subjects presenting with ACS, LVEF must be assessed during the index hospitalization (which may include during the index procedure by contrast left ventriculography) but prior to randomization in order to confirm the subject's eligibility.

8. Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if performed anytime >30 days before the index procedure, or between 24 hours and 30 days before the index procedure if successful and uncomplicated.

[28] Investigator should use discretion when enrolling subjects with high CHADS scores.

9. Subject requires future staged PCI either in target or non-target vessels or subject requires future peripheral interventions < 30 days after the index procedure.

10. Subject has received any solid organ transplants or is on a waiting list for any solid organ transplants.

11. At the time of screening, the subject has a malignancy that is not in remission.

12. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy.

13. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum.

14. Subject is receiving or will require chronic anticoagulation therapy (e.g., coumadin, dabigatran, apixaban, rivaroxaban or any other agent for any reason).

15. Subject has a platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3.

16. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B.

17. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2 or dialysis at the time of screening.[29]

18. Subject is high risk of bleeding for any reason; has a history of bleeding diathesis or coagulopathy; has had a significant gastro-intestinal or significant urinary bleed within the past six months.

19. Subject has had a cerebrovascular accident or transient ischemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g., aneurysm, arteriovenous malformation, etc.).

20. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used.

21. Subject has life expectancy < 5 years for any non-cardiac cause or cardiac cause.

22. Subject is in the opinion of the Investigator or designee, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason. This includes completion of Patient Reported Outcome instruments.

[29] Estimated GFR can be based on Modification of Diet in Renal Disease (MDRD) equation or Cockcroft-Gault equation (CCG).

23. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.[30]

24. Subject is part of a vulnerable population who, in the judgment of the investigator, is unable to give Informed Consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention.

6.3.2 Angiographic Eligibility Criteria

Assessment of angiographic eligibility is per visual assessment by an investigator both for qualitative and quantitative variables. IVUS, OCT or on-line QCA may be used if deemed necessary by investigators.

6.3.2.1 Angiographic Inclusion Criteria

1. One or two *de novo* target lesions:

    a. If there is one target lesion, a second non-target lesion may be treated but the non-target lesion must be present in a different epicardial vessel, and must be treated first with a successful, uncomplicated result prior to randomization of the target lesion.

    b. If two target lesions are present, they must be present in different epicardial vessels and both must satisfy the angiographic eligibility criteria.

    c. The definition of epicardial vessels means the LAD, LCX and RCA and their branches. Thus, the patient must not have lesions requiring treatment in e.g. both the LAD and a diagonal branch.

2. Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥ 50% and < 100% with a TIMI flow of ≥1 and one of the following: stenosis ≥ 70%, an abnormal functional test (e.g. fractional flow reserve, stress test), unstable angina or post-infarct angina.

    a. Lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.5 mm and ≤ 3.75 mm.

    b. Lesion(s) must be located in a native coronary artery with length by visual estimation of ≤ 24 mm.

[30] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

c. For Lead-In subjects with 3.0x18 mm Absorb BVS: lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.75 mm and ≤ 3.25 mm. The lesion length by visual estimation is ≥ 8 mm and ≤ 14 mm.

6.3.2.2 Angiographic Exclusion Criteria

All exclusion criteria apply to the target lesion(s) or target vessel(s).

1. Lesion which prevents successful balloon pre-dilatation, defined as full balloon expansion with the following outcomes:
   - Residual %DS is a maximum of < 40% (per visual estimation), ≤ 20% is strongly recommended.
   - TIMI Grade-3 flow (per visual estimation).
   - No angiographic complications (e.g. distal embolization, side branch closure).
   - No dissections NHLBI grade D-F.
   - No chest pain lasting > 5 minutes.
   - No ST depression or elevation lasting > 5 minutes
2. Lesion is located in left main.
3. Aorto-ostial RCA lesion (within 3 mm of the ostium).
4. Lesion located within 3 mm of the origin of the LAD or LCX.
5. Lesion involving a bifurcation with a:
   a. side branch ≥ 2 mm in diameter, or
   b. side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or
   c. side branch requiring dilatation.
6. Anatomy proximal to or within the lesion that may impair delivery of the Absorb BVS or XIENCE stent:
   a. Extreme angulation (≥ 90°) proximal to or within the target lesion.
   b. Excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion.
   c. Moderate or heavy calcification proximal to or within the target lesion. If IVUS used, subject must be excluded if calcium arc in the vessel prior to the lesion or within the lesion is ≥ 180°.
7. Vessel contains thrombus as indicated in the angiographic images or by IVUS or OCT.

8. Lesion or vessel involves a myocardial bridge.

9. Vessel has been previously treated with a stent at any time prior to the index procedure such that the Absorb BVS or XIENCE would need to cross the stent to reach the target lesion.

10. Vessel has been previously treated and the target lesion is within 5 mm proximal or distal to a previously treated lesion.

11. Target lesion located within an arterial or saphenous vein graft or distal to any arterial or saphenous vein graft.

6.4 Point of Registration

Lead-In subjects will be considered registered in the trial upon calling IVRS.

During the randomization phase, the subject is considered randomized after IVRS has been called and a device has been assigned (Absorb BVS or XIENCE). The subject is considered registered and in the ITT population at the point of randomization. Once randomization is completed and a treatment arm is assigned, crossover is not permitted. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment.

Registered subjects count toward the total sample size in ABSORB III. Refer to **Appendix IV** and **Figures 1 and 2** for further registration details.

6.5 Subject Discontinuation

Subjects who do not get registered in ABSORB III will be discontinued from the trial.

Missed Visits:

- If a subject misses one or more non-consecutive follow-up contact time points, the visit will be considered a missed visit and subject is not lost-to-follow-up.

- Under extenuating circumstances in which a subject cannot be contacted (e.g serious illness resulting in institutionalization, dementia, incarceration) indirect contact with a subject's healthcare provider or immediate family member identified will not be considered missed visits. Protocol required data will be collected in the electronic case report forms (eCRF). Subject may then return for subsequent visits.

Lost-to-Follow-up:

If the subject misses two consecutive scheduled follow-up time points, and the attempts to contact the subject or subject's healthcare provider or immediate family member detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject, including the following, at each contact time point:

- A minimum of two telephone calls to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact;

- If these attempts are unsuccessful, a certified letter should be sent to the subject.

Subject Discontinuation:

Every subject should remain in the Clinical Investigation until completion of the required follow-up period, however, a subject's participation in any Clinical Investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- **Subject Withdrawal:** Subject participation in a Clinical Investigation is voluntary and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time without loss of benefits or penalty.

- **Investigator Termination:** Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes it is necessary. Reasons for an investigator's termination of a subject include the following but are not limited to:

    - Per the investigator's discretion, a subject is unable to be compliant with the protocol requirement (e.g., medical conditions such as terminal cancer; subject moved out of the country, etc.)

    - Per the investigator's discretion, the follow-up study requirements (i.e., medications or procedures) may put the subject at risk.

- **Lost-to-Follow-up:** Subject does not complete the scheduled follow-up visits but has not 'officially' withdrawn from the clinical investigation.

Sponsor must be notified of the reason for subject discontinuation. The site will record this information on the eCRF and source documents. Investigators must also report this to their ethics committee (EC) or IRB as defined by their institution's procedure. Subjects will not be replaced.

The subject is considered to have completed the study upon Clinical Investigation completion of the 5-year follow-up.

However, if a subject withdraws from the study due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

7. TREATMENT AND EVALUATION OF SAFETY AND EFFECTIVENESS

7.1 Baseline

7.1.1 Baseline Laboratory Assessments to Confirm Subject Eligibility

Subject preparation will be in accordance with standard hospital policy for the care of interventional cardiology subjects.

7.1.2 Subject History

Subject history will include demographics (e.g., age, gender)[31], cardiac history including but not limited to Canadian Cardiovascular Society (CCS) and Braunwald classification of angina, history of myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, previous CABG and PCI, and concomitant cardiovascular medications (Refer to **Appendix II** for Definitions). In addition, measurements of weight, height, and resting blood pressure will be collected.

7.1.3 Patient-Reported Outcomes Assessment

All 2,000 primary analysis subjects in ABSORB III will complete the following Patient Reported Outcome questionnaires in person at the clinical site prior to the index procedure*.

- EuroQoL 5D (EQ-5D) survey to assess overall health status. The EQ-5D is a self-administered two-part instrument. The first part consists of 5 questions to assess current health state in 5 dimensions (mobility, self care, usual activities, pain/discomfort and anxiety/depression). The second part is a 20 cm visual analog scale that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state [31].

- Seattle Angina Questionnaire (SAQ) to assess disease-specific Quality of Life. The SAQ is a self-administered 19-item instrument designed to measure the physical and emotional effects of coronary artery disease across five dimensions (physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception)[32].

- Rose Dyspnea Scale (RDS) to assess severity of dyspnea. The RDS is a self-administered 4-item instrument designed to assess impact of dyspnea on health-related quality of life [33].

- Generalized Anxiety Disorder scale (GAD-7) to assess anxiety. The GAD-7 is a self-administered 7-item instrument designed to assess severity of patient's general anxiety disorder[34].

*Every effort should be made to have subjects complete all four patient reported outcomes questionnaires prior to the procedure. However, in situations where this is absolutely not

[31] Demographics include age, gender, post-menopausal status, date of birth, race/ethnicity, highest level of education, employment status and household income.

possible, subjects may complete them post-procedure, prior to discharge. Subjects who complete their questionnaires post-procedure should base their responses on their condition prior to the procedure.

7.2 Pre-Procedure

7.2.1 Pre-Procedure Laboratory Assessment

The following laboratory assessments need to be obtained prior to the index procedure or at the time of the index procedure depending on the assessment and condition of the subject.

Table 7.1 Baseline Laboratory Assessment

Within 21 days prior to procedure†	**Within 7 days prior to procedure**	**Within 48 hours prior to procedure€**
• Platelet and White Blood Count • Hemoglobin • Serum Creatinine • HbA1c‡ • Estimated GFR*	• Pregnancy test (if applicable)	• 12-lead ECG (within 24 hours preferred) • Creatine kinase (CK) • Creatine kinase myocardial-band isoenzyme (CK-MB)

†The 21 day labs must be known prior to index procedure.
‡ HbA1c is to be collected in diabetic subjects only, and its result is not needed prior to the index procedure.
€Within 24 hours must be done in cases in which there is evidence of acute or recent (<7 days) myocardial infarction (MI) or unstable angina; in these cases CK and CK-MB must be < ULN prior to the index procedure. For stable angina or silent ischemia, CK and CK-MB < ULN within 48 hours prior to index is acceptable. For stable angina subjects, if CK is > ULN but CK-MB is < ULN, with no signs of MI or unstable angina, the patient maybe enrolled. If the subject does not have a known diagnosis of MI or unstable angina within 96 hours prior to the index procedure, assessment of cardiac enzymes may be obtained from arterial blood drawn after the start of the index procedure but prior to device implantation. However, if CK-MB comes back elevated a protocol deviation will be issued.
* Glomerular Filtration Rate

Both CK and CK-MB must be measured pre-procedure and used to assess subject's eligibility criteria.

7.2.2 Dual Anti-Platelet Medications

Subjects selected for treatment with Absorb BVS or XIENCE must receive a loading dose of ≥ 300 mg of aspirin within 24 hours, regardless of whether the patient was previously taking aspirin. Subjects are also required to receive a loading dose of an ADP antagonist within 24 hours prior to the index procedure (preferred), but in all cases no greater than 1 hour after the end of the procedure. ADP antagonist administered must include one of the following, a peri-procedural loading dose of 600 mg of clopidogrel bisulfate, or 60 mg of prasugrel or 180 mg of ticagrelor. For patients with a recent ACS prior to admission, it is strongly recommended that the loading dose be given at least 6 hours before the procedure (clopidogrel 600 mg), or 1 hour prior to the procedure (prasugrel 60 mg or ticagrelor 180 mg), but in all cases no greater than 1 hour after the end of the procedure.

The prasugrel loading dose may be omitted for those subjects on chronic prasugrel therapy (5 or 10 mg daily, or according to prescribing information) for ≥ 7 days prior to the index procedure; however, it is recommended that a loading dose (≥ 30 mg) be re-administered. The ticagrelor

loading dose may be omitted for those subjects on chronic ticagrelor therapy (90 mg twice daily). For patients maintained on chronic clopidogrel, the loading dose of an ADP antagonist must be administered. A loading dose of prasugrel or ticagrelor may be safely given to patients maintained on chronic clopidogrel therapy, or even in those in whom a clopidogrel loading dose was recently administered. Ticlopidine may be used as a substitute at a dose in accordance with standard hospital practice only if the subject develops hypersensitivity or intolerance to clopidogrel, prasugrel, or ticagrelor.

Refer to respective prescribing information for ADP antagonist for further details regarding loading practice.

7.2.3 Anti-Coagulation Medications

Subjects must receive appropriate anticoagulation and other therapy according to standard hospital practice. Either unfractionated heparin or bivalirudin may be used for procedural anticoagulation, as per the discretion of the investigator. Subjects having been treated with low molecular weight heparin (LMWH) prior to the procedure must receive their last dose more than 8 hours prior to the index procedure. LMWH and fondaparinux are not permitted as procedural anticoagulants in this protocol.

Use of glycoprotein IIb/IIIa inhibitors will be at the discretion of the investigator. Any change in medication regime performed per the protocol, and not as routine hospital practice, can only occur after obtaining Informed Consent.

7.3 Index Procedure

7.3.1 Baseline (Pre-Procedure) Angiography

Baseline angiography of the target vessel(s) will be completed as per the Angiographic Core Laboratory Protocol.

7.3.2 Imaging Guidance Document

The Imaging Guidance Document will provide specific details and instructions from the angiographic, IVUS and OCT core laboratory regarding vessel sizing, and post-procedure and follow-up imaging with each respective modality. This document will be separate from the protocol.

7.3.3 Treatment of the Non-target Lesion(s)

In addition to target lesion, one additional non-target lesion in a different epicardial vessel can be treated by the specific country's regulatory-approved XIENCE stent (e.g., FDA-approved/CE-marked stent/Therapeutic Goods Administration (TGA)). A non-target lesion can be treated in the case that there are two lesions and one lesion does not meet the angiographic inclusion/exclusion criteria. The non-target lesions must be treated first, prior to randomization, and the subject may then only be randomized if treatment of the non-target lesion was successful and uncomplicated, defined as final diameter stenosis ≤ 10% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g., distal embolization, side branch closure), no chest pain lasting > 5 minutes,

and no ST segment elevation or depression lasting > 5 minutes. The non-target lesion will not be considered in the primary analysis.

7.3.4 Treatment Rules of the Target Lesion(s)

Prior to use, the Absorb BVS System or XIENCE should be inspected and prepared according to the IFU. The Absorb BVS System and XIENCE should be delivered and deployed per the IFU. The treatment strategy applies to all subjects in ABSORB III, including the Lead-In Phase and the Imaging Cohort.

- Treatment of a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel.
    - If a single target lesion is treated, it must be treated by the assigned device (Absorb BVS or XIENCE). For Lead-In subjects, the target lesion will be treated only with Absorb BVS.
    - If two lesions are treated, possible combinations are as follows:
        - Two target lesions:
            - If both lesions satisfy angiographic inclusion/exclusion criteria, then both lesions must be treated by the same device that the subject was randomized to (test device: Absorb BVS or control device: XIENCE),
            - For Lead-In subjects, both target lesions will be treated with Absorb BVS

OR

        - One target lesion and one non-target lesion:
            - If only one lesion satisfies angiographic inclusion and exclusion criteria then this lesion must be treated by the assigned device (test device: Absorb BVS or control device: XIENCE) as a target lesion and the other lesion must be treated by XIENCE as a non-target lesion per the *instructions for use* (IFU).
            - The non-target lesion must be treated first (before randomization) with a XIENCE, and the patient may then only be randomized if treatment of the non-target lesion was successful and uncomplicated, defined as final diameter stenosis ≤ 10% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g., distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes. Please refer to **Figure 2** in **Appendix V**.
            - For Lead-In subjects, one target lesion and one non-target lesion treatment is allowed. The target lesion must be treated by Absorb BVS, and the non-target lesion must be treated by XIENCE. The non-target lesion must be treated first and successfully (as defined above) before treating the target lesion with Absorb BVS.

Access Site and Guide Catheter Size:

- Either femoral or radial access may be used.
- A minimum 6F guide catheter or greater must be used during the index procedure per requirements for Absorb BVS implantation.
    - Minimum guiding catheter compatibility (inner diameter) for Absorb BVS is 0.070”/1.8 mm (6F) (refer to IFU).
    - Devices (i.e., guide sheaths such as the GuideLiner) that decrease the inner diameter of the guide catheter outside of the Absorb BVS minimum guide catheter compatibility must not be used with the Absorb BVS System. Do not insert a 5-in-6, or a 6-in-7 guide sheath into a 6F or 7F guiding catheter, respectively, as doing so will result in an inner diameter that is too small for use with the Absorb BVS.
    - If a guide sheath is necessary, the inner diameter must meet or exceed the above minimum guiding catheter requirements for Absorb BVS (i.e., only the 7-in-8 GuideLiner provides an adequate inner diameter (0.071” ID), 8F guide catheter would be required).
- For XIENCE, please follow IFU for the guiding catheter size.

Baseline Angiogram and Identification of the potential target lesion:

- Assessment of the potential target lesion(s) to be treated must be done to ensure angiographic criteria are met; this must occur prior to pre-dilatation and vessel sizing.

Pre-dilatation of potential target lesion

- Pre-dilatation of the potential target lesions(s) must be performed.
- Pre-dilatation must be performed with an angioplasty balloon; cutting or scoring balloons may be used per physician discretion, if the lesion appears to be mildly calcified.
- The pre-dilatation balloon should be sized 1:1 to the visually estimated RVD or 0.25 mm smaller than RVD. It cannot be more than 0.5 mm smaller than the visually estimated RVD of the target vessel. If pre-dilatation balloon is sized 1:1, a non-compliant balloon is strongly recommended.

  The pre-dilatation balloon must be equal in length or shorter than the planned scaffold/stent length.

  Important: Full balloon expansion with the pre-dilatation balloon must be achieved before the patient is randomized into the study. If there is any question that the target lesion was not fully dilated or that any significant resistance to expansion from the lesion remains, the lesion should be re-dilated with a non-compliant balloon (sized 1:1 to the RVD) at higher pressure. Absorb BVS or XIENCE must not be implanted in a lesion in which full balloon expansion has not been achieved.

- The potential target lesion must continue to meet angiographic criteria following adequate pre-dilatation, to be regarded as "successful pre-dilatation".
    - For randomized subjects, RVD remains ≥ 2.50 mm - ≤ 3.75 mm, and length of the lesion that will be covered by the device (including any edge dissections) is still ≤ 24 mm.
    - For Lead-In subjects, RVD remains ≥ 2.75 mm - ≤ 3.25 mm, and length of the lesion that will be covered by the device (including any edge dissections) is still ≥8- ≤ 14 mm.
    - Residual %DS is a maximum of < 40% (per visual estimation), ≤ 20% is strongly recommended.
    - TIMI Grade-3 flow (per visual estimation).
    - No angiographic complications (e.g. distal embolization, side branch closure).
    - No dissections NHLBI grade D-F.
    - No chest pain lasting > 5 minutes.
    - No ST depression or elevation lasting > 5 minutes.
- For two potential target lesions, the lesion with the higher possibility of failing vessel sizing criteria (per investigator's assessment) should be identified as the first target lesion and pre-dilated first before randomization.
    - If pre-dilatation of the 1st target lesion fails, the patient may not be randomized, and the interactive voice response system (IVRS) must not be called.
    - If the 1st target lesion was successfully pre-dilated and vessel sizing criteria are still met, the IVRS is called to randomize the subject. Once the first lesion is successfully treated[32] with the assigned device (and only at this time), the second target lesion must be pre-dilated, and then treated with the assigned device.
    - If the 1st target lesion was successfully pre-dilated but did not meet vessel sizing criteria, treat as a non-target lesion. Once the first lesion is successfully treated as a non-target lesion, the second lesion must be treated as the target lesion in which successful pre-dilatation and vessel sizing criteria must be met after which IVRS must be called and the target lesion treated per assignment. If 2nd target lesion fails pre-dilatation and vessel sizing criteria, it should be treated as non-target lesion and subject must not be randomized.
- Each target vessel and lesion should also be such that the operator believes either the Absorb BVS or XIENCE devices could be delivered to and cross the target lesion without additional lesion preparation (e.g., absence of excessive vessel or lesion tortuosity or calcification).

[32] Successful lesion treatment is defined as final diameter stenosis ≤ 30% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g. distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes.

Vessel Sizing

- Following the use of nitroglycerine (at least 100 µg intracoronary nitroglycerine, >150 µg preferred)[33] and successful pre-dilatation of the potential target lesion(s), vessel sizing must be conducted by visual estimation. Quantitative methods such as on-line QCA, IVUS or OCT may be used per physician discretion but are not required; taking into account that QCA tends to under-estimate RVD compared to visual estimation, whereas IVUS tends to over-estimate lumen RVD compared to visual estimation. Follow core laboratory guidelines for the use of each modality.

- Prior to randomization, IVUS or OCT can be used to evaluate the vessel if there is question regarding the eligibility of the vessel either before or after pre-dilatation.

- A subject must not be randomized in ABSORB III if

    - Vessel size or lesion length before or after pre-dilatation does not satisfy eligibility criteria.

    - Moderate or heavy calcification, tortuosity or other conditions are present proximal or within the target segment, reducing the likelihood that the Absorb BVS or XIENCE can be either delivered to or expanded at the lesion.

    - Complications and/or adverse events were identified during IVUS or OCT usage (e.g., vessel dissection NHLBI grade D-F).[34]

- Table 7.2 provides the guidance of vessel and device sizing during the procedure, which are detailed as the followings:

    - First, assess RVD based on visual estimation

    - Then, select a pre-dilatation balloon sized 1:1 to RVD or 0.25 mm smaller than RVD. For example, for RVD of 2.5 mm, a pre-dilatation balloon of 2.25-2.5 mm should be used.

    - Use the size of the inflated pre-dilatation balloon, as well as the results after pre-dilatation, to reassess the RVD for appropriate vessel sizing for the scaffold or stent. If the reassessed RVD after pre-dilatation exceeds the specified range for a specific BVS size, the next available size Absorb BVS can be used. For example, if the RVD is reassessed as 2.8 mm after pre-dilatation of a vessel that was believed to be 2.5 mm before pre-dilatation, then implant a 3.0 mm BVS.

    - Post-dilatation must always be a non-compliant balloon. Always make sure the non-compliant post-dilatation balloon has a length short enough so it is inflated within the scaffold margins to avoid edge dissection.

[33] If the patient's blood pressure is so low that ≥ 100 ug of nitroglycerine cannot be administered, the patient should not be randomized. It is suggested that ≥200 µg of nitroglycerine be administered if the systolic blood pressure is >140 mmHg. Timing of nitroglycerine administration and pre-dilatation is per physician discretion, but must be before randomization and assessment of scaffold or stent size.

[34] Examples of complications associated with IVUS or OCT: side-branch occlusion, persistent S-T abnormalities, prolonged chest pain, flow limiting dissections etc.

Table 7.2 Vessel and Device Sizing

Closest RVD by Visual Estimation	Pre-dilatation Balloon Diameter	Reassessed Closest RVD after Pre-dilatation	Absorb BVS Diameter
2.5 mm	2.25 or 2.5 mm	2.5 mm	2.5 mm
2.75 mm	2.25 – 2.75 mm	2.75 mm	3.0 mm
3.0 mm	2.5 – 3.0 mm	3.0 mm	3.0 mm
3.25 mm	2.75 – 3.25 mm	3.25 mm	3.5 mm
3.5 mm	3.0 – 3.5 mm	3.5 mm	3.5 mm
3.75 mm	3.25 – 3.75 mm	3.75 mm	3.5 mm

Randomization

- Upon successful treatment of the non-target lesion (if any) and completion of successful pre-dilatation and vessel sizing of the first target lesion, interactive voice response system (IVRS) can be called.
- A subject is considered registered and in the ITT population at the time of randomization.
- Lead-In subjects will not be randomized but are assigned to Absorb BVS treatment in target lesion(s).

Lesion Treatment

- The length of the Absorb BVS and XIENCE stent should be selected to allow at least 2 mm but less than 4 mm of normal or nearly normal reference vessel at each edge.
- If the Absorb BVS cannot reach or cross the lesion or additional lesion preparation is required, the Absorb BVS must be removed and a new Absorb BVS must be introduced after subsequent pre-dilatation(s) with the same sized or larger non-compliant balloon at higher pressure. Note: the Absorb BVS should not be "Dottered" across the lesion if it does not cross easily.
- If the Absorb BVS is unable to reach or cross the target lesion after multiple attempts (maximum of two Absorb BVS; including additional lesion preparation), a XIENCE stent must be used.
- If XIENCE is unable to reach or cross the target lesion after multiple attempts (including additional lesion preparation), the investigator should treat the lesion per standard of care.
- In the case of two target lesions assigned to the Absorb BVS, if the first lesion is unsuccessfully treated with the Absorb BVS the following must occur:
    - First target lesion must be treated with XIENCE. If the treatment of the 1st target lesion is successfully treated with XIENCE, treat the 2nd target lesion with Absorb BVS.
    - If the treatment of the 1st target lesion is unsuccessful treated with XIENCE, treat the 1st lesion and 2nd lesion per standard of care. The subject must not be treated with a BVS.

- Every attempt must be made that the two lesion treatment occur at the same index procedure as staged procedures are not allowed. However, if a staged procedure does occur BVS must not be used.

- Successful lesion treatment is defined as final diameter stenosis ≤ 30% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g. distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes.

- For Absorb BVS, the scaffold should be deployed slowly, by pressurizing the delivery system in 2 atm increments each, over 5 seconds, until the scaffold is completely expanded. Pressure should be maintained for 30 seconds if tolerated by the patient.

- For the Absorb BVS and XIENCE delivery balloon, do not exceed the rated burst pressure (RBP) per the IFU for the individual device.

- Post-dilatation of target lesion or non-target lesion treated with XIENCE should be per standard of care.

- If post-dilatation of the target lesion treated with Absorb BVS is necessary the following guidance is given:

  - A low profile, high pressure, non-compliant, balloon dilatation catheter that has not been previously inflated must be used.

  - The post-dilatation balloon length should be selected such that the balloon stays within the margins of the scaffold so as to avoid an edge dissection.

  - The expanded diameter of the post dilatation balloon must be within the allowable expansion limits of the scaffold. Do not dilate the Absorb BVS beyond the dilatation limit which is 0.5 mm above the nominal diameter. Doing so may result in scaffold damage. Thus, it is highly recommended that the compliance chart of the non-compliant balloon selected must be carefully reviewed prior to dilatation and an appropriate maximum pressure used to ensure that the scaffold is not over-dilated.

Table 3.0 Scaffold Diameter and Maximum Diameter Limit

Nominal Scaffold Diameter	Post Dilatation Maximum Diameter Limit
2.5 mm	**3.0 mm**
3.0 mm	**3.5 mm**
3.5 mm	**4.0 mm**

  - The delivery balloon cannot be removed from the body and reinserted and used for post-dilatation

- IVUS or OCT guidance may be used as per standard of care.

- Please refer to the physician training deck for user guidance in handling procedural issues (e.g., difficult in recrossing an implanted scaffold for purposes such as intravascular imaging or post-dilatation if needed).

Imaging Cohort

If subject is in the Imaging Group (See **Appendix VI and Imaging Guidance Document** for further details):

- Post-procedure angiography, IVUS and OCT are required based on respective imaging groups.

- If post-dilatation was performed, post-procedure imaging must be conducted following last balloon inflation.

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.

7.3.5 Bailout Stenting or Alternative Procedures

Bailout procedures may be performed if the subject experiences:

- Dissection requiring intervention

- Occlusive complication as evidenced by a decrease in target vessel flow

- Chest pain or ischemic changes measured by ECG that do not respond to repeat balloon inflations, medical therapy or lytic agents

- Unplanned additional device is required to cover the target lesion

In the randomized subjects, if a bailout device is required for a target lesion (e.g., for edge dissection), the same device as the implanted device must be used. Overlap of the bailout stent/scaffold with the implanted stent/scaffold should be 1-2 mm. Gaps should be avoided.

  - o Use Absorb BVS if target lesion is treated with Absorb BVS.

  - o Use XIENCE if target lesion is treated with XIENCE.

  - o If a bailout with an Absorb BVS device cannot be delivered to the site of the lesion, the device should be carefully withdrawn and a XIENCE used.

  - o If an appropriate size Absorb BVS is not available XIENCE can be used.

If during the Lead-In phase a bailout is required, the investigator should use an appropriately sized XIENCE stent and not an Absorb BVS.

The Imaging Cohort subjects that receive metallic stent bailout of an Absorb BVS treated lesion will be required to complete imaging follow-up at the protocol specified time points of 3 years for IVUS or OCT, depending on which imaging group the subject is in. However, the subject's imaging data will not be included in the imaging study analysis and will not be counted towards the associated powered secondary endpoints analysis. These subjects may be replaced by another subject that received an Absorb BVS without metallic stent overlap.

IMPORTANT: It is required that the bailout device be placed so that there is no visible gap between the Absorb BVS and the bailout device. In such a case, at least 1 mm (minimum) to 2 mm (maximum) overlap is required.

IMPORTANT: In the rare event of acute occlusion following Absorb BVS placement, the bailout device should be XIENCE and deployed within the Absorb BVS such that the Absorb BVS is completely covered by the bailout device if this is believed to be in the best interest of the patient.

Although a bailout procedure is not considered a major adverse cardiac event (MACE) unless the subject sustains death, emergent CABG, PCI or MI, such procedures should be avoided unless required for safe subject management.

7.3.6 Final (Post-procedure) Angiography

Angiographic imaging will also be performed after the Absorb BVS or XIENCE stent deployment. Physicians should follow accepted hospital imaging practice to ensure good apposition of the Absorb BVS or XIENCE to the vessel wall. For angiographic imaging, post-implantation images should be captured the same orthogonal views that were used for the pre-procedure images. Intracoronary nitroglycerine should be re-administered before final angiography.

7.3.7 Final (Post-procedure) IVUS and OCT

For subjects not required to have post-procedure imaging, IVUS and OCT may be performed post-procedure if the investigator believes there is incomplete apposition of the device. The procedure will be performed according to the site's standard. However, if malapposition is seen and post-dilatation required, a non-compliant balloon should be used and in the case of Absorb BVS, do not dilate the Absorb BVS beyond the dilatation limit which is 0.5 mm above the nominal diameter. Repeat angiography in orthogonal views must be performed after any additional inflations.

7.3.8 Imaging Assessment

Subjects from the Imaging Cohort will receive angiography (includes vasomotion assessment), IVUS and OCT at pre-specified time-points (**Section 7.5**). Imaging assessments should be conducted per core lab guidelines in the Imaging Guidance Document distributed to each site. Intracoronary nitroglycerine should be given before all imaging runs to avoid spasm and afford maximal luminal dimensions.

Any Imaging Cohort subject that did not receive the assigned Absorb BVS or XIENCE stent will not receive follow-up imaging procedures. These subjects will be clinically followed under the study. If an Imaging Cohort subject had a TLR prior to the imaging follow-up, the imaging data at the time of TLR and at the protocol specified later imaging time points will be analyzed but not included in the imaging endpoint analysis. If an Imaging Cohort subject had a TVR or angiogram prior to the imaging follow-up, the subject will continue to have the protocol specified imaging follow-up and will not be replaced. If an Imaging Cohort subject has two target lesions but only one target lesion was successfully treated with the assigned device, the unsuccessfully treated target lesion must be imaged post-treatment and at the specified follow-up

times only if the assigned study device was implanted for lesion treatment. Imaging Cohort subjects that receive metallic stent bailout of an Absorb BVS treated lesion will be required to complete imaging follow-up at the protocol specified time points of 3 years for IVUS or OCT, depending on which imaging group the subject is in. However, the subject's imaging data will not be included in the imaging study analysis and will not be counted the associated powered secondary endpoints. These subjects may be replaced by another subject that received an Absorb BVS without metallic stent overlap.

7.3.8.1 QCA of Target Vessel

- QCA will be performed pre-procedure, post-procedure and at the 3-year follow-up for the imaging study subjects.
- Angiography must be performed per the angiographic core laboratory guidelines.

7.3.8.2 IVUS Pull-back of Target Vessel

- IVUS pullback (20 MHz or 40-45 MHz catheter can be used) is required post-procedure and at 3-year follow-up for the imaging study subjects.
- Pullback of the IVUS catheter should be performed from the distal reference to the guiding catheter, per IVUS core laboratory guidelines.
- If IVUS reveals any findings such that additional PCI is performed, an additional IVUS run must be performed after the last intervention.
- **Caution:** It is important to place the IVUS transducer in the center of the lumen to avoid lifting or disturbing the device struts during pullback.

7.3.8.3 OCT of the Target Vessel

- OCT pullback is required post-procedure and at 3-year follow-up for the imaging study subjects.
- OCT pullback should contain at least one recognizable landmark, usually a major side branch.
- **Caution:** It is important to place the OCT transducer in the center of the lumen to avoid lifting or disturbing the device struts during pullback.

7.3.8.4 Vasomotion Assessment

- At the 3-year follow-up, assessment of vessel movement in response to nitroglycerin infusion will be conducted. Please see the Imaging Guidance Document for the details of this assessment.
- Vasomotion assessment should not be assessed under the following conditions, and those subjects may be replaced for the imaging analysis:

- Target lesion treated with Absorb BVS with metallic stent overlap
- Target lesion undergoing other PCI procedures prior to 3-year imaging follow-up
- If target lesion has ≥ 50% stenosis at the time of the 3-year assessment and does not clearly require revascularization, FFR should be conducted to determine if lesion is flow limiting. If the lesion is flow limiting and requires revascularization, vasomotion assessment should not be done.

- Details regarding the angiographic assessment of the vessel and timing of nitroglycerine infusion are further detailed in the Imaging Guidance Document.

7.4 Post–procedure

7.4.1 Post-procedure Information to be Recorded

The following information needs to be obtained between 12 hours following the index procedure and hospital discharge (in-hospital stay is considered to be a maximum of 7 days following the index procedure).

Between 12 hours post-procedure and discharge

- Date of discharge
- Antiplatelet medications
- Chronic concomitant medications
- Adverse Events, if any

7.4.2 Post-procedure Laboratory and Clinical Tests

The following laboratory assessments need to be obtained between post-index procedure and hospital discharge. Hospital discharge cannot occur prior to 16 hours to ensure complete post-procedure cardiac enzyme collection.

IMPORTANT: These tests must be performed whether or not they are considered part of the Investigator's standard of clinical practice.

Post-procedure and discharge

- A 12-lead ECG must be obtained between 30-90 minutes post procedure.
- Both Creatine kinase (CK) and Creatine kinase myocardial-band isoenzyme (CK-MB) must be obtained for ALL registered subjects as it will be used for cardiac assessment of subjects post-index procedure
  - Pre-procedure CK and CK-MB draw*
  - First post-procedure CK and CK-MB draw at 6 to 12 hours post-procedure.

- Second post-procedure CK and CK-MB draw at 18-24 hours post-procedure, or at the time of discharge as long as discharge is at or after 16 hours post-procedure**.

- If either of the post-procedure CK-MB levels are ≥ 3 x ULN, serial CK and CK-MB levels must be drawn until they are falling.

* If the patient has stable coronary artery disease, the pre-procedure level can be obtained during procedure but prior to stent/scaffold deployment. If the patient has a recent acute coronary syndrome, the pre-procedure level must be obtained prior to the procedure and the CKMB shown to be within normal limits prior to the patient being randomized.

** For hospitals required to discharge stable subjects prior to 16 hours, the subject may be discharged but will have to return to the enrolling institution for their second biomarker draw.

CK and CK-MB levels are required at all time points. If troponin is collected at the pre-procedure or post-procedure time points, this should also be documented in the electronic case report forms

7.4.3 Follow-up Antiplatelet Medications

All subjects will be maintained at a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients) or 90 mg twice daily of ticagrelor for a minimum of 12 months following the procedure. For prasugrel subjects < 60 kg in weight or ≥75 years of age, a maintenance dose of 5 mg per day for 12 months is allowable. Patients with prior stroke or TIA should receive clopidogrel or ticagrelor, not prasugrel. All subjects must receive between ≥75 to ≤ 100 mg of aspirin daily through 5 years follow-up during the study and should continue to take aspirin indefinitely.

Refer to respective prescribing information for ADP antagonist for further details regarding maintenance dose.

The start of anti-platelet medications, any changes or discontinuation of the medications, as well as the reasons for those change will be documented in the eCRF.

7.4.4 Other Chronic Concomitant Medications

Administration of concomitant medications other than any approved ADP antagonist and aspirin are not required in this protocol/CIP. Subjects may receive other medications as needed per physician's discretion. These concomitant medications must be recorded if the medications are expected to continue for more than 3 months. However, antiplatelet medications must be recorded regardless of duration.

The use and changes for the following classes of chronic concomitant medications, including dosage, frequency and route of administration should be recorded.

- Cardiovascular Medications: Angiotensin converting enzyme inhibitors and angiotensin receptor blockers, renin inhibitor, beta blockers, calcium channel blockers, diuretics, coumadin, other chronic anticoagulants or anti-platelet agents (e.g. rivaroxaban, apixaban, dabigatran, cilostazol), vasodilators, statins, and other lipid lowering agents

- Non-cardiovascular Medications: Systemic anti-inflammatory medications, hormone replacement therapy and diabetic medications

7.5 Clinical and Imaging Follow-up for All Subjects

Clinical follow-up will be performed periodically at the following intervals for all subjects:

- 30 ± 7 days follow-up telephone contact/office visit
- 180 ± 28 days follow-up telephone contact/office visit
- 1 year ± 28 days office visit and ECG[35]
- 2 years ± 28 days follow-up telephone contact/office visit
- 3 years ± 28 days follow-up telephone contact/office visit
- 4 years ± 28 days follow-up telephone contact/office visit
- 5 years ± 28 days follow-up telephone contact/office visit

Registered subjects must be clinically followed even if no assigned device is implanted. Clinical follow-up visits can also be conducted by a blinded Nurse Practitioner or Physician Assistant that has been trained to the protocol.

For the 2,000 primary analysis subjects of ABSORB III, Patient Reported Outcome follow-up assessments will be conducted as the followings:

- 30 ± 7 days follow-up, in-person, mail, or phone (EQ-5D, SAQ, RDS, GAD-7)
- 1 year ± 28 days office visit (EQ-5D, SAQ, RDS, GAD-7)
- 2 years ± 28 days follow-up, in-person, mail, or phone (EQ-5D, SAQ, RDS, GAD-7)
- 3 years ± 28 days follow-up, in-person, mail, or phone (EQ-5D, SAQ, RDS, GAD-7)
- 5 years ± 28 days follow-up, in-person, mail, or phone (EQ-5D, SAQ)

The questionnaires will be mailed to the subject for completion or can be completed during the phone or office visit. If questionnaires are mailed to the subjects, the subjects must mail the questionnaires back to the clinical site.

[35] ECG can be obtained outside of the investigational site but must be reviewed by one of the site investigators and obtained within the protocol visit window. If an investigator suspects that a subject, with a negative ECG, will require a diagnostic angiogram due to possible cardiac symptoms, a functional study must be performed prior to the angiogram to confirm whether the patient has ischemia. This must be done whether or not it is a site standard, due to the use of the ARC definition to adjudicate ischemia driven revascularization.

In addition to the clinical follow-up, imaging follow-up will be performed at the following intervals for the Imaging Cohort:

- Post-procedure: angiography and IVUS (~150 subjects) or angiography and OCT (~50 subjects)
- 3 years ± 28 days follow-up office visit and ECG: subjects in the Imaging Cohort (n=150) will receive follow-up angiography and IVUS.
- 3 years ± 28 days follow-up office visit and ECG: subjects in the Imaging Cohort (n=50) will receive follow-up angiography and OCT.

Imaging Cohort subjects are required to undergo only one of the imaging follow-up time-points.

The following information will be collected at each of the time points:

- Any adverse events*, medications, laboratory tests and 12-lead ECGs, if performed;
- Any repeat coronary angiography and results of such, if applicable;
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG);
- Use and compliance of medications per clinical investigation plan;
- Use and changes in concomitant cardiovascular medications.

* All adverse events must be collected up to and including to the 1 year follow up for all 2250 subjects. Following the 1-year follow-up, it is mandatory to collect information on cardiac adverse events, device related adverse events and on serious adverse events.

7.6 Additional Follow-up Visits for All Subjects

Additional subject visits, such as unscheduled visits, may occur as clinically warranted. The following information will be collected:

- Assessment of angina status
- Adverse events
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Use and compliance to protocol medications (aspirin and prasugrel/clopidogrel/ ticagrelor/ticlopidine)
- Use and changes in chronic concomitant medications (Refer to **Appendix II** for definition)

For unscheduled visits for suspected ischemic cardiac events, sites should make reasonable efforts to obtain cardiac enzymes (Troponin I or T), CK and CK-MB, and/or ECG if the site is aware of the visit at the time of its occurrence. In all other scenarios (i.e., site does not become

aware until after the fact), no protocol deviation will be issued if Troponin I or T, CK and CK-MB, and/or ECG were not obtained at the time of the unscheduled visit.

All efforts must be made to obtain follow-up information on subjects who have undergone procedures or have been treated for adverse events in a non-trial-related hospital(s).

All coronary revascularizations must be classified prospectively by the investigator as ischemia-driven or not ischemia-driven (Refer to **Appendix II** for definition). If a subject has a coronary revascularization, all clinical information such as symptoms or lack of symptoms of ischemia, and possible relations with the target lesion/vessel should be fully recorded in the source documents prior to angiogram.

8. ADVERSE EVENTS

8.1 Definitions

To comply with worldwide standards and guidelines on clinical trial adverse event reporting, AV has developed the below definitions to be used and adhered to by the investigators. The exact definitions as referenced in these standards and guidelines are included in appendix II.

8.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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

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

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.1.2 Serious Adverse Event

If the adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE):

a. led to death,

b. led to serious deterioration in the health of the subject, that either resulted in

   1. a life-threatening illness or injury, or

   2. a permanent impairment of a body structure or a body function, or

3. in-patient or prolonged hospitalization, or

4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c. led to fetal distress, fetal death or a congenital abnormality or birth defect

An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

8.1.3 Device Deficiency/Product Experience

Device deficiency (DD) is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

Product Experience (PE) is defined as any expression of customer concern or dissatisfaction, including adverse events and patient issues that occurred during or after the use of a commercially available medical device.

8.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more likely cause.

8.2.1 Unanticipated Serious Adverse Device Effect

Unanticipated serious adverse device effect (USADE) refers to any serious adverse device 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.

8.3 Adverse Event/Device Deficiency/Product Experience Reporting

8.3.1 Adverse Event and Serious Adverse Event Reporting

All AEs will be collected on each registered subject through the 1-year follow-up visit. After 1 year, only the following will be collected:

- All serious AEs
- All cardiovascular events regardless of seriousness or device relationship
- All trial device-related events and events for which the relationship to the trial device is unknown
- All unanticipated adverse device effects
- All Cerebral Vascular Accidents (CVAs)

The Investigator will monitor the occurrence of adverse events for each registered subject during the course of the clinical trial/investigation. Adverse Events reported by the subject, observed by the Investigator, or documented in medical records should be recorded on the adverse event eCRF, whether believed by the Investigator to be related or unrelated to the investigational device implant as required by this protocol.

A fax form will be made available to allow the investigator to report SAEs and device deficiencies in the event the entry cannot be made in the EDC (FRM2073001 SAE Notification Form). This does not replace the EDC reporting system, however, all information must still be entered in the EDC system as soon as feasible.

For all registered patients, AEs (any new event/experience that was not present at baseline or worsening of an event present at baseline) will be collected as required by this protocol. The reporting of AEs will start when the guiding catheter enters the subject's vasculature. Reported AEs will be monitored through the course of the trial. Additional information with regards to an AE should be updated within the appropriate case report form.

Unchanged, chronic, non-worsening or pre-existing conditions are not adverse events and should not be recorded on the adverse event eCRF.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Study site	**Reporting timelines**
All Study Sites	SAEs must be reported no later than 3 calendar days from the day the study personnel becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware that the event met the criteria of a serious adverse event must be recorded in the source document. The investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system. However they need to be reported on the SAE Notification Form (FRM2073001).

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the EDC System is not available. This does not replace the EDC reporting system. All information must still be entered in the EDC system once the system is back to normal function.

8.3.2 UADE/USADE Reporting to Sponsor and IRB

Abbott Vascular requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

8.3.3 Device Deficiency/Product Experience Reporting

All device deficiencies/product experiences should be reported within the EDC System on the appropriate eCRF. A fax form will be made available to allow the investigator to report device deficiencies in the event that the entry cannot be made in the EDC (FRM2073000 Device Deficiency Report Form). This does not replace the EDC reporting system. However, all information must still be entered in the EDC system as soon as feasible. In case a device deficiency occurred before the patient ID and randomization number has been assigned, the device deficiency should be reported to the sponsor via a Device Deficiency Report Form (FRM2073000).

The investigator should report all DDs/PEs to the Sponsor as soon as possible but no later than outlined below.

Study sites	Reporting timelines
All Study Sites	DDs/PEs must be reported no later than 3 calendar days from the day the study personnel becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The device, if not implanted or not remained in the subject, should be returned to Abbott Vascular.

Device deficiencies should be reported to the IRB/EC per the investigative site's local requirements.

8.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and DDs/PEs to the country regulatory authority, per local requirements.

8.4 Safety Monitoring by Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will serve in an advisory role to Abbott Vascular to ensure safety by reviewing cumulative data from the clinical trial at pre-scribed intervals for the purpose of safeguarding the interests of trial participants. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on safety data, the DSMB may consider a recommendation for modifications or termination of the

trial based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to trial modifications rest with Abbott Vascular.

9. ADJUDICATION OF EVENTS

9.1 The Clinical Events Committee (CEC)

The Clinical Events Committee is comprised of qualified physicians who are not investigators in the trial. The Clinical Events Committee is responsible for adjudicating specified clinical endpoints based on the specific criteria used for the categorization of clinical events in the trial. The composition, guiding policies, and operating procedures governing the CEC are described in a separate CEC Manual of Operations.

9.2 Angiographic Core Laboratory

The angiographic core laboratory will be responsible for reviewing all available follow-up coronary angiograms for registered subjects, to determine if a revascularization was performed by PCI, and if so, whether or not the revascularization was related to the target lesion, target vessel or non-target vessel. The data from angiographic core laboratory will be provided to CEC for adjudicate stent thrombosis events with angiographic follow-up.

10. STATISTICAL ANALYSIS

10.1 Statistical Overview

The ABSORB III trial is powered based on the primary endpoint of TLF at 1-year. TLF is defined as a per-subject hierarchical count of cardiac death, target vessel Q-wave or non-Q-wave MI (per protocol-defined MI definition, Appendix II), or ischemia-driven target lesion revascularization (ID-TLR).

The primary endpoint of TLF at 1 year will be evaluated using the difference in event rates in the ITT population. The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the primary endpoint with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{PE}$

H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{PE.}$

TLF_{Absorb} and TLF_{XIENCE} are the 1-year TLF rates in the Absorb BVS and XIENCE arms, respectively. Δ_{PE} is the non-inferiority margin for the primary endpoint.

The likelihood score method by Farrington and Manning will be performed for the NI test. A successful trial requires a p-value less than 0.025 from this NI test.

Based on the SPIRIT IV data for the non-complex XIENCE V subjects, the 1-year TLF rate per the primary analysis definition is approximately 6.1% (N~2000) for all of the core sizes of XIENCE V stents. To account for the variability in this study, the assumed 1-year TLF rate for

XIENCE V is set to be the upper limit of the one-sided 95% confidence interval based on the above SPIRIT IV data and this leads to an event rate of 7%. The assumed true rate for Absorb BVS is also 7%. The NI margin derived per FDA guidance is 4.5%.

The remaining secondary clinical endpoints in **Section 5.3** will be descriptively compared using the estimated rates and two-sided 95% confidence limits. P values will be shown for hypothesis-generating purposes.

Study Success

Study success is defined as passing the non-inferiority test of Absorb BVS to XIENCE on the primary endpoint of TLF at 1 year.

10.2 Analysis Populations

10.2.1 Intent-to-Treat Population

The ITT population is defined as the subjects registered in the study at the point of randomization, regardless of the treatment actually received. Subjects will be analyzed in the treatment group to which they were randomized. Subjects enrolled but not randomized will not be included in the ITT population.

10.2.2 Per Treatment Evaluable Population

The per-treatment evaluable (PTE) population will consist of subjects who have received only study device(s) (Absorb BVS or XIENCE) at the target lesion. Analyses based on the per-treatment-evaluable population will be as "treated". Subjects will be included in the treatment group corresponding to the study device actually received. The PTE population will exclude subjects with the protocol deviations to the following criteria:

- General inclusion criteria:
    - #3 Subject must have evidence of myocardial ischemia (e.g., stable, unstable angina, post-infarct angina or silent ischemia) suitable for elective PCI. Subjects with stable angina or silent ischemia and < 70% diameter stenosis must have objectives sign of ischemia as determined by one of the following, echocardiogram, nuclear scan, ambulatory ECG or stress ECG). In the absence of noninvasive ischemia, fractional flow reserve (FFR) must be done and indicative of ischemia.
- General exclusion criteria:
    - #1 Any surgery requiring general anesthesia or discontinuation of aspirin and/or an ADP antagonist is planned within 12 months after the procedure.
    - #3 Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to clopidogrel and prasugrel and ticagrelor; or to heparin and bivalirudin, and therefore cannot be adequately treated with study medications.

- #4 Subject had an acute myocardial infarction (AMI: STEMI or NSTEMI) within 72 hours of the index procedure and both CK and CK-MB have not returned to within normal limits at the time of index procedure; or subject with stable angina or silent ischemia has CK-MB that is greater than normal limits at the time of the index procedure.

- #5 Subject is currently experiencing clinical symptoms consistent with new onset AMI (STEMI or NSTEMI), such as nitrate-unresponsive prolonged chest pain with ischemic ECG changes.

- #7 Subject has a left ventricular ejection fraction (LVEF) < 30% assessed by any quantitative method, requires future staged PCI either in target or non-target vessels.

- #8 Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if performed anytime >30 days before the index procedure, or between 24 hours and 30 days before the index procedure if successful and uncomplicated.

- #9 Subject requires future staged PCI either in target or non-target vessels or subject requires future peripheral interventions < 30 days after the index procedure.

- #17 Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2 or dialysis at the time of screening

- All angiographic inclusion and exclusion criteria

- Select treatment strategy:

    - Non-target lesion treatment not per protocol

    - Target lesion treated not per protocol

    - Pre-dilatation not done per protocol

    - ≥1 target lesion(s) in which different devices were used in each lesion – semi-crossover.

    - Treatment of > 2 lesions or two lesions in the same vessel

    - Subject enrolled after unsuccessful treatment of non-target lesion

10.3 Sample Size Calculations and Assumptions

10.3.1 ABSORB III Primary Endpoint

The sample size calculation for the primary endpoint of TLF at 1-year follow-up is based on the following assumptions:

- One-sided non-inferiority test

- $\alpha = 0.025$
- Randomization ratio is 2 (Absorb BVS arm) : 1 (XIENCE arm)
- The true TLF rate is assumed to be 7.0% for both the Absorb BVS arm and the XIENCE arm
- Non-inferiority margin (delta) of 4.5%

Based on the above assumptions, a total of 1,900 subjects (1,267 for the Absorb BVS arm and 633 for the XIENCE arm) will provide approximately 96% power. Assuming a 5% dropout rate at 1 year (which is a common assumption for contemporary trials), approximately 2,000 subjects will be enrolled.

The primary endpoint will be assessed on all 2000 randomized subjects in ABSORB III.

10.3.2 Powered Secondary Endpoints

When the non-inferiority test of the primary endpoint TLF at 1 year is passed, superiority tests of the Powered Secondary Endpoints will be performed based on a pre-specified testing sequence. The pre-specified testing sequence will ensure the control of study wise type-I error rate at 0.05. For further details refer to the statistical analysis plan (SAP).

Imaging Cohort Powered Secondary Endpoint 1

The in-stent/scaffold mean lumen area change (ΔMLA) from post-procedure to 3 years by IVUS (mean lumen area is to be measured after nitrate infusions) will be evaluated using the difference between the two means of the two treatment arms in the pooled subjects from the Imaging Cohort of ABSORB III and ABSORB Japan. Superiority testing will be performed with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

H_0: $\Delta MLA_{Absorb} - \Delta MLA_{XIENCE} = 0$

H_A: $\Delta MLA_{Absorb} - \Delta MLA_{XIENCE} \neq 0$.

ΔMLA_{Absorb} and ΔMLA_{XIENCE} are the in-stent/scaffold mean lumen area changes in the Absorb BVS and XIENCE arms, respectively.

The sample size calculation is based on the following assumptions:

- The in-stent/scaffold mean lumen area change at 3 years for the Absorb BVS arm is assumed to be 0.5 ± 1.69 mm^2
- The in-stent/scaffold mean lumen area change at 3 years for the XIENCE arm is assumed to be -0.4 ± 1.17 mm^2
- Two-sided alpha= 0.05
- ~150 subjects from the Imaging Cohort in ABSORB III, 50% IVUS follow-up rate at 3 years

- ~150 subjects from ABSORB Japan, 70% IVUS follow-up rate at 3 years
- ~15% of all subjects will have dual target lesion treatment.

An effective sample size of 207 lesions (138 for the Absorb BVS arm and 69 for the XIENCE arm) will provide approximately 99.4% power using two sample t-test.

The sample size calculation was performed using NCSS PASS 2008 (Hintze JL, 2002. PASS User's Guide-II. NCSS).

Imaging Cohort Powered Secondary Endpoint 2

The in-stent/scaffold mean lumen diameter change (ΔMLD) between pre- and post-nitrate infusion at 3 years by angiography will be evaluated using the difference between the means of the two treatment arms in the pooled subjects from the Imaging Cohort of ABSORB III and ABSORB Japan. Superiority testing will be performed with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

H_0: $\Delta MLD_{Absorb} - \Delta MLD_{XIENCE} = 0$

H_A: $\Delta MLD_{Absorb} - \Delta MLD_{XIENCE} \neq 0$.

ΔMLD_{Absorb} and ΔMLD_{XIENCE} are the in-stent/scaffold mean lumen diameter changes in the Absorb BVS and XIENCE arms, respectively.

The sample size calculation is based on the following assumptions:

- The in-stent/scaffold mean lumen diameter change at 3 years for the Absorb BVS arm is assumed to be 0.054 ± 0.156 mm (based on 3-year imaging data from the Absorb Cohort B trial).
- The in-stent/scaffold mean lumen diameter change at 3 years for the XIENCE arm is assumed to be 0.018 ± 0.052 mm (based on clinical assumptions as no imaging data for XIENCE is available)
- Two-sided alpha= 0.05
- ~200 subjects from the Imaging Cohort in ABSORB III, 50% angiographic follow-up rate at 3 years
- ~400 subjects from ABSORB Japan, 80% angiographic follow-up rate at 3 years
- ~15% of all subjects will have dual target lesion treatment

An effective sample size of 483 lesions (322 for the Absorb BVS arm and 161 for the XIENCE arm) will provide approximately 96.2% power using two sample t-test.

The sample size calculation was performed using NCSS PASS 2008 (Hintze JL, 2002. PASS User's Guide-II. NCSS).

Powered Secondary Endpoint for Angina

Angina at 1 year (exclude angina following the index procedure through discharge, not to exceed a period of 7 days) will be evaluated using the difference between the angina rates of the two treatment arms. Superiority test will be performed with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

H_0: $ANGINA_{Absorb} - ANGINA_{XIENCE} = 0$

H_A: $ANGINA_{Absorb} - ANGINA_{XIENCE} \neq 0$.

$ANGINA_{Absorb}$ and $ANGINA_{XIENCE}$ are the 1-year angina rates in the Absorb BVS and XIENCE arms, respectively.

Using a two-sided alpha of 0.05, assuming 5% lost to follow-up at 1 year, the trial will have approximately 90% power to demonstrate superiority with a difference of 6.3% between the Absorb BVS arm and the XIENCE arm (e.g. 16.3% in the Absorb BVS arm vs. 22.6% in the XIENCE arm) using Pearson's Chi-square test.

The powered secondary endpoint of angina at 1 year will be assessed on the primary analysis group in ABSORB III, separate from the Lead-In Group and the Imaging Cohort Subjects.

The sample size calculations were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Powered Secondary Endpoint for All Revascularization

All revascularization at 1 year will be evaluated using the difference between the all revascularization rates of the two treatment arms. Superiority test will be performed with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

H_0: $ALLREVASC_{Absorb} - ALLREVASC_{XIENCE} = 0$

H_A: $ALLREVASC_{Absorb} - ALLREVASC_{XIENCE} \neq 0$.

$ALLREVASC_{Absorb}$ and $ALLREVASC_{XIENCE}$ are the 1-year all revascularization rates in the Absorb BVS and XIENCE arms, respectively.

Using a two-sided alpha of 0.05, assuming 5% lost to follow-up at 1 year, the trial will have approximately 90% power to demonstrate superiority with a difference of 3.6% between the Absorb BVS arm and the XIENCE arm (e.g. 3.6% in the Absorb BVS arm vs. 7.2% in the XIENCE arm) using Fisher's Exact test.

The powered secondary endpoint of all revascularization at 1 year will be assessed on the primary analysis group in ABSORB III, separate from the Lead-In Group and the Imaging Cohort Subjects.

The sample size calculations were performed using NCSS PASS 2008 (Hintz JL, 2002. PASS User's Guide-II NCSS).

Powered Secondary Endpoint for ID-TVR

ID-TVR at 1 year will be evaluated using the difference between ID-TVR rates of the two treatment arms. Superiority test will be performed with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses for the superiority test are:

H_0: $IDTVR_{Absorb} - IDTVR_{XIENCE} = 0$

H_A: $IDTVR_{Absorb} - IDTVR_{XIENCE} \neq 0$.

$IDTVR_{Absorb}$ and $IDTVR_{XIENCE}$ are the 1-year ID-TVR rates in the Absorb BVS and XIENCE arms, respectively.

Using a two-sided alpha of 0.05, assuming 5% lost to follow-up at 1 year, the trial will have approximately 80% power to demonstrate superiority with a difference of 2.3% between the Absorb BVS arm and the XIENCE arm (e.g. 1.8% in the Absorb BVS arm vs. 4.1% in the XIENCE arm) using Fisher's exact test.

The powered secondary endpoint of ID-TVR at 1 year will be assessed on the primary analysis group in ABSORB III, separate from the Lead-In Group and the Imaging Cohort Subjects.

The sample size calculations were performed using NCSS PASS 2008 (Hintze JL, 2002. PASS User's Guide-II. NCSS).

Powered Secondary Endpoint for Diabetic Indication

To assess the performance of Absorb BVS in the diabetic subgroup by testing against the corresponding pre-specified analysis.

To support this powered secondary endpoint, Abbott Vascular intends to pool ABSORB family studies. Refer to SAP for details.

10.4 Statistical Analyses

Non-inferiority testing of the primary endpoints will be one-sided and performed at a 0.025 significance level for the comparison of the Absorb BVS arm with the XIENCE arm. Superiority tests on the powered secondary endpoints will be performed at a two-sided 0.05 significance level. Analyses of other secondary endpoints will be descriptive in nature.

For binary variables such as TLF, TLR, and clinical procedure success, counts, percentages, and 95% confidence intervals will be calculated, and p-values may be presented for hypothesis generating purposes. Pearson's Chi-squared test or Fisher's exact test will be performed when appropriate. In addition, logistic regression will be performed to determine whether the baseline characteristics exhibit any trends in predicting TLF.

For continuous variables such as age, means, standard deviations, and 95% confidence intervals for the mean will be calculated and p-values may be presented for hypothesis generating purposes. For time-to-event variables, such as time to TLF, survival curves will be constructed using Kaplan-Meier estimates, and log rank test results will be displayed. Unless specified, analyses will be performed with pooled data across all study sites.

For further details refer to the statistical analysis plan (SAP).

10.4.1 Primary Endpoint Analysis

The ABSORB III primary endpoint of TLF at 1-year follow up will be analyzed for the ITT and the PTE populations. The primary analysis will be based on the ITT population. The non-inferiority hypothesis testing will be performed using a non-inferiority test statistic by Farrington and Manning. Non-inferiority of Absorb BVS to XIENCE will be established if the p-value for the non-inferiority test is less than 0.025.

In order for ABSORB III to be successful, the primary analysis with the NI test should meet the pre-specified criterion.

10.4.2 Powered Secondary Endpoint Analyses

Analysis of the Powered Secondary Endpoints for angina, for all revascularization, for ID-TVR, and for diabetic indication will include subjects from the primary analysis group. Pearson's Chi-square test will be used for superiority testing based on the ITT and PTE populations for the powered secondary endpoint for angina. Fisher's exact test will be used for superiority testing based on the ITT and PTE populations for the powered secondary endpoints for all revascularization and for ID-TVR. Analysis of the Imaging Cohort Secondary Endpoints 1 and 2 will include pooled subjects from the Imaging Cohort of ABSORB III and ABSORB Japan. Two sample t-test will be used for superiority testing based on the ITT and PTE populations.

Details of the analyses for the powered secondary endpoints can be found in the statistical analysis plan (SAP).

10.4.3 Secondary Endpoint Analyses

Secondary endpoints other than the powered endpoints described above will be summarized descriptively for the ITT population. For further details refer to the statistical analysis plan (SAP).

10.4.4 Additional Analyses

Adverse Events related to stent/scaffold thrombosis, vascular complications or bleeding complications, and their relation with antiplatelet therapies used in the trial will be investigated between the two treatment groups, if applicable.

Descriptive analyses will be provided for the Lead-In subjects.

For further details refer to the SAP.

10.4.5 Exploratory Analyses

Details on pre-specified exploratory analyses can be found in the SAP.

10.4.6 Informational Endpoint Analyses

Patient Reported Outcomes for the 2,000 primary analysis subjects in ABSORB III will be analyzed for informational purpose.

10.4.7 Subgroup Analysis

Pre-specified subgroups such as diabetes, sex, age will be examined. Further details can be found in the SAP.

Pre-specified pooled analysis will be performed comparing the diabetic subgroup vs. non-diabetic subgroup in the Absorb BVS arm by combining Absorb BVS data from the Abbott Vascular Absorb BVS programs. Further details can be found in the SAP.

10.4.8 Handling of Multiplicity Issues

Methods to handle multiplicity are specified, in the SAP.

10.4.9 Criteria for Early Termination of the Trial for Effectiveness

No formal statistical rule for early termination of the trial for effectiveness is defined.

10.4.10 Procedures for Accounting for Missing, Unused or Spurious Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the final report. Sensitivity analysis of the primary endpoint of TLF at 1-year follow-up will be performed using the Kaplan-Meier estimates. If missing data for the primary analysis is greater than 5% for any treatment arm, imputation methods may be utilized as the sensitivity analyses.

10.4.11 Pooling Strategy

Details on pooling strategy can be found in the SAP.

10.4.12 Deviations from the Original Statistical Plan

Any major changes to the statistical plan (available upon request) will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents for trial-related monitoring, audits, IRB/MEC review, and regulatory inspections.

Subjects providing Informed Consent agree to allow the Sponsor or designee access and copying rights to pertinent information in their medical records relevant to trial participation (the Investigator should ensure patient identifiers are removed for medical records that are copied). The Investigator will obtain, as part of the Informed Consent, permission for trial monitors or regulatory authorities to review at the investigative site, in confidence, any records identifying the subjects in this clinical trial/investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information as per local data protection laws.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Selection of Clinical Sites and Investigators

The sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the assigned device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Primary Investigator at the site.

12.2 Training

12.2.1 Site Training

All Investigators/trial personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone training may take place as required. Training of Investigators/trial personnel will include, but is not limited to, the protocol requirements, investigational device usage, electronic case report form completion and trial personnel responsibilities. All Investigators/trial personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigator/trial personnel must not perform any trial-related activities that are not considered standard of care at the site.

12.2.2 Training Required for the Use of the Test Device

Investigators will be trained on the use of the Absorb BVS System. Please refer to **Section 4.2 ABSORB Physician Training.**

12.2.3 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the protocol, eCRFs and investigational device usage (as appropriate). Documentation of this training will be according to written procedures.

12.3 Monitoring

Sponsor and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan which will include the planned extent of source data verification

12.3.1 Designated Monitors

Study monitors are individuals who are designated to oversee the progress of a study. These individuals are appropriately trained and qualified to monitor the progress of a clinical study. The study sponsor may designate additional monitors at any time during the study. The Sponsor should be contacted for additional information on the person(s) responsible for monitoring activities.

12.3.2 Visits

Prior to initiating any procedure, the sponsor monitor (or delegate) will visit each investigator to ensure that the following criteria are met:

The Investigator understands and accepts the obligation to conduct the research study according to the protocol and applicable regulations, and has signed the Investigator Agreement or the Clinical Study Agreement.

The Investigator and his staff have sufficient time and facilities to conduct the study and that they have access to an adequate number of appropriate subjects to conduct the study.

Source documentation must be available to substantiate proper Informed Consent procedures, adherence to protocol procedures, adequate reporting and follow-up of Adverse Events, accuracy of data collected on Case Report Forms, and device information.

The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or Research Coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

12.4 Deviations from Protocol

It is the Investigator's responsibility to ensure that there are no deviations from the protocol **without prior notification and approval of the sponsor** and that all actions are in full compliance with all established procedures of the IRB/EC or equivalent committee. The Investigator will not deviate from the protocol for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor. In subject-specific deviations from the protocol, a Protocol Deviation Case Report Form will be completed. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the protocol and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all Protocol Deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event that an Investigator does not comply with the Investigator Agreement or the Clinical Study Agreement or protocol, the Investigator will be notified of the site’s non-compliance.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor’s monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the Investigator
- Telephoning the Investigator

- Corresponding with the Investigator

Repeated non-compliance with the signed agreement, the protocol or any other conditions of the study may result in further escalation in accordance with the Sponsor's written procedures including securing compliance or, at its sole discretion, the Sponsor may terminate the Investigator's participation in the study.

12.5 Quality Assurance Audits

The Sponsor may conduct periodic Quality Assurance audits (on-site audits) at various clinical trial/investigation sites. A Sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a Quality Assurance audit. The Investigator and Research Coordinator must be available to respond to reasonable requests and queries made during the audit process.

12.6 Sponsor Support to Clinical Trial/Investigation Site for Regulatory Body Inspection

In the event that an Investigator is contacted by a Regulatory Agency in relation to this clinical trial/investigation, the Investigator will notify the Sponsor immediately and IRB/MEC as appropriate. The Investigator and Research Coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical trial/investigation (e.g., Form FDA 483, Inspectional Observations, and warning letters). The Sponsor may provide any needed assistance in responding to regulatory inspections.

12.7 Committees

12.7.1 Steering Committee

The Steering Committee is assigned by the Sponsor and comprises the Study Chairman and Principal Investigators, as specified on the cover page of this protocol. Other physician scientists may be added to the steering committee. The Sponsor will be represented by at least one person each from the Clinical Science and Clinical Program Management groups. The directors of the core laboratories and other Sponsor's personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the Sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the study. This committee will meet regularly to monitor patient enrollment, general data collection and non-compliance with the investigation plan at individual centers, to review and act upon recommendations of the Data and Safety Monitoring Board, to review operational issues that may arise and warrant a protocol amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the study.

12.7.2 Publications Committee

The Publication Committee is composed of representatives from Abbott Vascular Clinical Research, Steering Committee, Investigators, and other personnel as determined by the Steering Committee. This team will oversee presentation and/or publication aspects of the study. The

Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from study generated data. The committee will also review all external requests for accessing study related data and strategies aligning with Abbott Vascular presentation and publication team expectations. The committee will also follow Abbott Vascular applicable policies and Standard Operating Procedures.

12.7.3 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group that does not have any affiliation with Abbott Vascular, the Investigators or core laboratories. Details regarding the DSMB were reported earlier in **Section 8.4**.

12.7.4 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the trial. Details regarding the CEC were reported earlier in **Section 9.1**.

13. DATA HANDLING AND RECORD KEEPING

Abbott Vascular Data Management will perform all data management activities including documentation of the systems and procedures to be used. All eCRF data collection will be performed through a secure web portal and all authorized personnel with access to the electronic data capture (EDC) system must use an electronic signature access method to enter, review or correct data. Electronic signature procedures shall comply with the CFR Title 21 Part II and the ICH Guidelines for Good Clinical Practice (GCP) (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential.

All eCRF data will be downloaded from the EDC system and reformatted into a data structure acceptable to Abbott Vascular. The data will be subjected to consistency and validation checks within the EDC system and will be subject to supplemental validation following download. Completed eCRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the Investigator's site and a backup copy archived with Abbott Vascular

For the clinical trial/investigation duration, the Investigator will maintain complete and accurate documentation including but not limited to medical records, clinical trial/investigation progress records, laboratory reports, electronic Case Report Forms, signed Informed Consent Forms, device accountability records, correspondence with the IRB/MEC and clinical trial/investigation monitor/Sponsor, Adverse Event reports, and information regarding subject discontinuation or completion of the clinical trial/investigation.

13.1 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's medical records that corroborates data collected on the Case Report Forms. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject's record, at a minimum, and if applicable to the investigation:

- Medical history/physical condition of the subject before involvement in the trial sufficient to verify protocol entry criteria

- Dated and signed notes on the day of entry into the trial referencing the sponsor, protocol number, subject ID number and treatment assigned (does not apply to blinded randomized trials) and a statement that informed consent was obtained

- Dated and signed notes from each subject visit (for specific results of procedures and exams)

- Adverse Events reported and their resolution including supporting documents such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of Investigator's device relationship assessment of SAEs

- Study-required laboratory reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results

- Notes regarding protocol-required and prescription medications taken during the trial (including start and stop dates)

- Subject's condition upon completion of or withdrawal from the trial

- Any other data required to substantiate data entered into the eCRF

13.2 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and /or clinic chart reviews will be performed clearly and accurately by site personnel trained on the protocol and eCRF completion. eCRF data will be collected for all patients that are registered into the trial.

13.3 Record Retention

The sponsor will archive and retain all documents pertaining to the study for the lifetime of the device under evaluation.

The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical trial/investigation records.

13.4 Investigational Devices

13.4.1 Investigational Device Accountability

Abbott Vascular ships investigational devices (Absorb BVS System) only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site. In geographies using the commercially available CE marked device, the investigators will acquire the product through their normal commercial vendors.

The Investigator will maintain adequate records of the receipt and disposition of the investigational device, including part number and serial number, date used, patient ID number and treating physician. An Inventory Accountability Log supplied by the Sponsor will be used. The Inventory Accountability Report must document the disposition of all investigational devices including those that have been returned to Sponsor. In sites using commercially available CE marked devices (XIENCE and Absorb BVS), the primary investigator will maintain records of device usage for the study subjects. The records will contain device part number and serial number, date implanted, patient identification number, and implanting physician.

Use of any investigational device outside of the protocol is strictly forbidden because the Investigator has access to other commercially available PCI catheters and may constitute grounds for removal of the Investigator/site from the clinical trial/investigation. In geographies using the commercially available CE marked device, the commercial device may be used in non-trial patients.

All investigational devices that are associated with a device failure or device deficiencies must be returned immediately to the Sponsor.

14. ETHICAL CONSIDERATION

14.1 Institutional Review Board/Medical Ethics Committee Review

Institutional Review Board (IRB)/Medical Ethics Committee (MEC) approval for the protocol and Informed Consent Form /other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to participation in this clinical trial/investigation. The approval letter must be signed by the IRB/MEC Chairman or authorized representative prior to the start of this clinical trial/investigation and a copy must be provided to the Sponsor. No changes will be made to the protocol or Informed Consent Form or other written information provided to the patient without appropriate approvals, including IRB/MEC, the Sponsor, and/or the regulatory agencies.

Until the clinical trial/investigation is completed, the Investigator will advise his/her IRB/MEC of the progress of this clinical trial/investigation, per IRB/MEC requirements. Written approval must be obtained annually from the IRB/MEC to continue the clinical trial/investigation, according to each institution's IRB/MEC requirements (US studies only). Further, any amendments to the protocol as well as associated Informed Consent Form changes will be submitted to the IRB/MEC and written approval obtained prior to implementation, according to each institution's IRB/MEC requirements.

No investigative procedures other than those defined in this protocol will be undertaken on the registered subjects without the written agreement of the IRB/MEC and the Sponsor.

15. PUBLICATION POLICY

The data and results from the trial are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical trial. The Investigators will not use the clinical trial/investigation-related data without the written consent of the Sponsor for any other purpose than for clinical trial/investigation completion or for generation of publication material, as referenced in the clinical trial/investigation Site

Agreement. The publication and/or presentation of results from a single clinical trial/investigation site are not allowed until publication and/or presentation of the multi-center results. The Sponsor acknowledges that the trial's Principal Investigators intend to publish a multi-center publication regarding the clinical trial/investigation results, and numerous secondary publications. The Sponsor must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the clinical trial/investigation Site Agreement.

The Sponsor will be responsible for determining whether to register the Clinical Investigation on www.clinicaltrials.gov <<http://www.clinicaltrials.gov>> or any other clinical investigations, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the trial should be registered, Sponsor shall be responsible for any such registration and results posting as required by Clinical Trials.gov. Institution and/or Principal Investigator(s) shall not take any action to register the trial.

16. RISK ANALYSIS

16.1 Potential Risk

16.1.1 Cardiac Catheterization, Stenting and Percutaneous Transcatheter Coronary Angioplasty

Refer to Investigator Brochure and/or Instructions for Use for this section for both Absorb BVS and XIENCE for the associated risks.

Refer to APPENDIX VIII: for the Risk stratification of Cardiac Catheterization, Stenting and Percutaneous Transcatheter Coronary Angioplasty

16.1.2 Associated Risks of the Absorb BVS Polymer

The Absorb BVS is composed of a backbone fabricated from poly (L-lactide) and a drug-eluting coating layer which is a mixture of poly (DL-lactide) and the drug, everolimus. These polymer materials were selected based on their long history of use in approved medical devices and their mechanical properties. Examples of currently approved bioabsorbable polymers used for clinical vascular applications include the Angio-Seal vascular closure device and the Igaki-Tamai bioabsorbable stent. In addition, PLA is widely used in orthopedic implants and cosmetic treatment.

The Angio-Seal device is composed of a plug of collagen sponge and an absorbable polymer anchor that are connected by an absorbable positioning suture. The Angio-Seal device leaves the polymer anchor inside the vessel at the end of the procedure. The anchor is held in place against the vessel wall by the absorbable suture. The polymer anchor is manufactured from a 50/50 copolymer of DL-lactide and glycolide. The Angio-Seal device has a much more rapid degradation profile than the Absorb BVS, and has a much higher mass than the Absorb BVS. Thus, it is an excellent example supporting the fact that the polymer and its degradation products are well tolerated by blood vessels [21, 35].

The Igaki-Tamai bioabsorbable stent was the first to provide clinical trial data with biodegradable PLLA stent in humans [12]. The stent is manufactured from a monofilament poly (L-lactide) fiber wound into a helical pattern. The long-term safety data presented by this clinical study demonstrates that the PLLA is a safe polymer for use in intravascular applications [17, 19]. Igaki-Tamai peripheral stent was evaluated in the PERSEUS clinical trial [21], of which results supported approval for CE mark (November 29, 2007).

The coating polymer, poly (D,L-Lactide), is the same polymer used for the Abbott Vascular Champion drug eluting stent project and in the FUTURE I and FUTURE II human clinical trials conducted by BioSensors. Safety of this polymer was demonstrated in the FUTURE I and FUTURE II trials [36-38], The Champion project also collected a substantial body of evidence that demonstrated the coating polymer is safe to use in a vascular application.

Systemic reaction possibly caused by PLLA orthopedic implant was rarely reported [39]. Local/regional/systemic delayed adverse effects caused by PLLA injection in cosmetic treatment was infrequent [40].

In summary, safety and biocompatibility of the Absorb BVS has been demonstrated based upon biocompatibility testing per ISO 10993-1, numerous preclinical animal safety studies, and the long use of these polymers in medical implants. While the long-term outcome of the Absorb BVS is unknown at present, follow-up through 5 years from the ABSORB Cohort A and 2-year follow-up from ABSORB Cohort B, has shown a low occurrence of clinical events.

16.1.3 Everolimus

Refer to Investigator Brochure and/or Instructions for Use for this section for both Absorb BVS and XIENCE for the associated risks.

16.1.4 Drug Interaction of Everolimus

Refer to Investigator Brochure and/or Instructions for Use for this section for both Absorb BVS and XIENCE for the associated risks.

16.1.5 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The carcinogenicity, genotoxicity, and reproductive toxicity of Absorb BVS have not been evaluated; however, long term carcinogenicity and teratology studies were performed with the XIENCE V, a similar Everolimus-eluting coronary stent system. In the carcinogenicity studies, XIENCE V was implanted subcutaneously in transgenic mice. Based on the results of this study, XIENCE V does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks. In the reproductive toxicity studies XIENCE V was implanted in rats and showed no effect on their fertility or reproductive capability. Additionally, there were no teratogenic effects in the offspring in this study.

There is no carcinogenicity, genotoxicity, and reproductive toxicity in PLA, lactide, and lactic acid.

Pregnancy/Fertility

There are no adequate studies in pregnant women or men intending to father children regarding the safety of everolimus or the Absorb BVS. Everolimus when administered at oral doses of 0.1 mg/kg and above showed effects on pre- and post-natal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Therefore, pregnant and nursing subjects and those planning pregnancy up to one year following the index procedure are excluded from this study. Female subjects with childbearing potential enrolled in this study must have a negative pregnancy test done within 7 days prior to the index procedure. If a female subject does get pregnant, the risks to the fetus are unknown. Effective contraception must be used before implanting an Absorb BVS. The method of contraception is a personal choice but needs to be made with respect to the subject's values with adequate medical information on the effectiveness and safety of the method. Except for surgical removal of the uterus and ovaries or total abstinence, all methods of birth control have a failure rate. Intrauterine devices (IUD), hormonal contraceptives (birth control pills, injections or implants), tubal ligation or partner's vasectomy and barrier contraceptives (condoms, diaphragms, and cervical caps) are available means of birth control. The primary care provider or a gynecologist should be consulted concerning the best birth control method for the subject given his/her medical history and lifestyle choices.

Lactation

It is unknown whether everolimus is distributed in human milk. Everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to the implantation of Absorb BVS, a decision should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

16.1.6 Risks associated with Quantitative Imaging Modalities

Subjects registered in ABSORB III may receive IVUS or OCT during the index procedure. Complication rates of IVUS range from 1 to 3%, transient spasm being the most common which is treated with intracoronary nitroglycerin. The rate of major complications, dissection or MI, is less than 0.5%. Examination of imaged vessels compared with non-imaged vessels shows no significant damages or disease progression at 1 year follow-up [41, 42]. Other complications include bleeding at the entry puncture site, injury to the vascular wall, thrombosis of the vessel, and peripheral embolization. Retrospective studies of cardiac patients show no increase in complications between non-imaged vessels and imaged vessels and IVUS is demonstrated to be safe for multiple uses (up to 6) after sensitive procedures [42].

OCT is not commonly associated with major adverse events; most events can be minimized through appropriate training. Procedural planning and full education of risks associated with investigating vulnerable plaques will further minimize risk [43].

Intracoronary nitroglycerin will be used during the index procedure in ABSORB III. Intracoronary nitroglycerin (NTG) is usually routinely administered to these patients in order to prevent coronary spasm for optimum imaging results. It has been shown that coronary dilatation occurs with as little as 5 μg of intracoronary NTG and that moderate doses of 50-200 μg can still produce vasodilatation without systemic effects such as hypotension or reflex tachycardia [44]. The known contraindications to nitroglycerin include among others hypersensitivity, recent use

of phosphodiesterase-5 inhibitors like sildenafil (Viagra), narrow angle glaucoma, and symptomatic hypotension. Further information about the risks of nitroglycerin can be found in its Summary of Product Characteristics (SPC).

16.2 Risk Management Procedure

The risks and benefits of PCI with the control device, XIENCE, are well understood and documented in the XIENCE IFU. The XIENCE will remain in the coronary artery lesion indefinitely unless it is surgically removed. The adverse events and potential device issues associated with the test device, the Absorb BVS System, are not fully understood. The safety of the Absorb BVS for the treatment of coronary artery disease has been studied in ABSORB Cohort A and ABSORB Cohort B trials. Although ABSORB Cohort A and ABSORB Cohort B did not compare the treatment of Absorb BVS to XIENCE, the data provides preliminary support that the safety of implanting Absorb BVS is no different than the safety of implanting the control device as long as the IFUs for both devices is followed. With the use of the Absorb BVS, there is the potential for device issues and adverse events not previously identified to occur.

The long term safety and the efficacy of Absorb BVS in the treatment of coronary artery disease has also been evaluated in ABSORB Cohort A and ABSORB Cohort B. Currently, there is no long-term data comparing Absorb BVS to XIENCE, however a descriptive comparison between the ABSORB Cohort B outcomes and the SPIRIT FIRST trial using data from the 3.0x18 mm XIENCE V only, have shown similar results between Absorb BVS and XIENCE V (**Section 2.2**). Further studies are needed to confirm this. The long term pathology of the coronary artery lesion after treatment with the Absorb BVS continues to be evaluated and the long-term benefits of Absorb BVS are not fully understood and continue to be evaluated.

Subjects will receive 75 mg of clopidogrel bisulfate (Plavix®) daily or 10 mg of prasugrel daily or 90 mg twice daily of ticagrelor (or according to prescribing information [45]) for a minimum of 1 year to reduce the risk of thrombosis and to provide extended protection to compensate for potentially delayed endothelialization after implant. Subjects will also receive aspirin ≥ 75 to ≤ 100 mg to be taken indefinitely. The side effects from aspirin are well documented and commonly include allergic reactions; gastrointestinal irritation such as stomach pain, dyspepsia, gastritis; and bleeding.

Prasugrel [46] can cause significant, sometimes fatal bleeding. The use of prasugrel in subjects at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischemic events are deemed to outweigh the risk of serious bleedings. This concern applies especially to subjects who: have a propensity to bleed, are ≥ 75 years of age, a body weight < 60 kg, have concomitant use of medications that increase the risk of bleeding, or are likely to undergo urgent coronary artery bypass graft surgery. Compared to patients weighing ≥ 60 kg, patients weighing < 60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. The label recommends that patients weighing < 60 kg be placed on a maintenance dose 5 mg daily. Prasugrel is contraindicated for subjects who have: hypersensitivity to the active substance or to any of the excipients, active pathological bleeding, history of stroke or transient ischaemic attack (TIA), or severe hepatic impairment (Child-Pugh class C). Further information about the risks of prasugrel can be found in its Summary of Product Characteristics (SPC).

Ticagrelor [47] can cause significant, sometimes fatal bleeding. Compared to clopidogrel, ticagrelor increased the overall risk of bleeding to a somewhat greater extent. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs). The increase in bleeding risk was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased. Dyspnea was reported more frequently with ticagrelor than with clopidogrel. Ticagrelor is contraindicated for subjects who have: history of intracranial hemorrhage, active pathological bleeding, and severe hepatic impairment. Further information about the risks of ticagrelor can be found in its Summary of Product Characteristics.

Prasugrel and ticagrelor are indicated for patients with acute coronary syndrome. The use of these medications outside the approved conditions may be associated with risks. Subjects will be monitored closely throughout the trial duration.

The device should only be used by physicians who have been trained in interventional cardiology. The selected investigators will be trained on the device prior to participating in the study. In addition, they and other hospital personnel who are participating in a clinical trial will be trained on the IFU and clinical trial protocol.

The patients will be screened against the inclusion and exclusion criteria before enrollment in the trial. The patients will be evaluated clinically with or without imaging at pre-determined time points per clinical trial protocol requirements to assess their clinical status.

Corrective and preventative actions will be implemented by Abbott Vascular, as necessary, if deviations from recommendations in the protocol or IFU are observed.

All device deficiencies, commercial complaints, and adverse events from clinical trials are monitored internally by Abbott Vascular. An independent Data Safety Monitoring Board (DSMB) will monitor safety throughout the clinical trial. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

16.3 Potential Benefit

The Absorb BVS is intended to revascularize the vessel like a conventional metallic stent, provide controlled elution of anti-proliferative drug to minimize neointimal growth and then resorb naturally into the body after vessel healing and remodeling are complete.

The imaging and vasomotion data from ABSORB Cohort A at 2 years and ABSORB Cohort B at 1 year showed the potential for vessel movement with the ABSORB BVS in response to pharmacological stimuli (**Section 2.1.9**). Lumen patency was maintained as shown with an increase in IVUS average lumen area in ABSORB Cohort A at 2 years and maintained average lumen area in ABSORB Cohort B at 2 years (**Section 2.1.9**).

Another benefit of Absorb BVS is that non-invasive imaging can be done using multislice computed tomography (MSCT) to evaluate stenosis of treated lesion. The Absorb BVS scaffold is radiolucent and was undetected by MSCT apart from the platinum markers at each end of the scaffold. In 24 subjects of ABSORB Cohort A, the scaffolded vessel segment at 2 years were

qualitatively patent. The 18-month clinical and MSCT results for the full ABSORB Cohort B trial (Cohort B1 and B2, 101 patients) were reported at the TCT congress in November, 2011. Unlike metal stents, on MSCT scans at 18 months it was possible to assess quantitatively the scaffolded segment in 61 of the 72 scans performed. These results provided an early indication that non-invasive imaging is feasible with the Absorb BVS System, which could reduce patient burden.

17. SPECIAL POPULATIONS

Women and minorities in the US are known to have low PCI utilization [48] . Recent statistics show that from 1984 to 2004, despite an increase in PCI utilization followed by a plateau, women have lower PCI utilization compared to men [48]. There are also data to support that women have a higher risk of PCI related mortality compared to men [49, 50] . The poorer outcomes among women have been related to delayed onset of disease, co-morbidities, vessel size associated with smaller body surface area, and premature coronary artery disease [49]. However, in the advent of advanced PCI technology, outcomes have improved among women and benefits of stenting can be applied to both women and men [49, 51, 52]. In SPIRIT III trial gender sub-analysis women treated with XIENCE V and TAXUS had worse MACE outcomes compared to men [52]. However, the difference in 1 year MACE rates between women and men was not significant in the XIENCE arm (p=0.146) but was significant in the TAXUS arm (p=0.019) [52]. A recent XIENCE V USA gender sub-analysis, which consisted of a larger population than SPIRIT III, found comparable ARC stent thrombosis (0.85% vs. 0.82%), cardiac death and MI (3.7% vs. 2.9%), and TLR (5.0% vs. 4.2%) rates among women compared to men treated with XIENCE V.

Certain minority populations are found to have a higher rate of heart disease and associated risk compared to whites in the US. The prevalence of coronary heart disease (CHD) and MI is highest in black males and females compared to white males and other minority groups [53] . Among the US minority population, blacks and Hispanics compared to whites and Asian, have the lowest PCI utilization rates [48]. Blacks and Hispanics that undergo PCI are found to be younger, and have co-morbidities such as diabetes, hypertension, obesity, and renal failure, compared to whites [54]. There has been some limited evidence that indicated these differences did not result in different angioplasty outcomes across minority groups [54]. However, a recent retrospective analysis in a small population (n=1438) which was 47.4% black, reported a higher MACE (death, MI and TVR) rate (21.7%) at 2.9 years compared to non-blacks (13.6%) [55]. Furthermore, after adjusting for age, comorbidities and socioeconomic status, black race remained an independent predictor of MACE [55].

Overall women and minorities in the US have been identified as populations shouldering a greater coronary artery disease burden but ironically lower PCI utilization. However, there is evidence, albeit limited, to demonstrate that these populations may have poorer outcomes compared to other groups, while still benefiting from PCI utilization. Based on the discordance between disease burden and PCI utilization, it becomes imperative for PCI clinical trials to increase women and minority participation.

To increase recruitment of special populations in ABSORB III, Abbott Vascular will implement several strategies. The first being a recruitment brochure that will educate patients on heart disease risk and the difference in heart disease burden across ethnicity and genders. This brochure will also inform patients that they can speak to their physician about whether they are

eligible to enroll in ABSORB III. Patients interested in the trial will also be shown a detailed flip-chart, presented by the site explaining the procedure and possible treatments received if they enroll in the trial.

A second recruitment strategy will be compensation to subjects for their participation in ABSORB III (US only). Abbott Vascular will provide payments to subjects in order to compensate them for their time and effort in returning to the hospital or otherwise responding to Trial-related follow-up questions. Subjects' participation in-person in the visits at the time points indicated below will be compensated as set forth below. Payment will be made to Institution as a pass-thru to the subject on a per-subject per-time point basis, following completion of all eCRF data entry for the given procedure or receipt of imaging films at the core laboratory, depending on the nature of the visit, receipt of an invoice from Institution and evidence of the payment by Institution to the applicable subject. Institution will make payment by check to each eligible subject. This reimbursement is subject to IRB approval. All subjects at the baseline visit will be paid $50.00. Subjects who complete the 1-year follow-up will receive $100. IVUS imaging subjects who complete the 3-year follow-up will receive $500. OCT imaging subjects who complete the 3-year follow-up will receive $500.

Lastly, subjects enrolled in the trial identified by the Institution or the Primary Investigator as having a financial hardship will be reimbursed for the protocol-required antiplatelet (Clopidogrel, Prasugrel, Ticagrelor, or Ticlopidine) regimen.

Abbott Vascular believes these strategies may aid in the recruitment of patients from special populations that may not traditionally participate in a clinical trial.

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym or Abbreviation	Complete Phrase or Definition
%DS	percent diameter stenosis
ACS	Acute Coronary Syndrome
AE	adverse event
AMI	acute myocardial infarction
BVS	bioresorbable vascular scaffold
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society (Canada)
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	clinically-indicated
CIP	Clinical Investigation Plan (EU)
CK	creatine kinase
CK-MB	creatine kinase myocardial-band isoenzyme
CoCr	cobalt chromium
CRA	Clinical Research Associate
CRF	case report form
CSA	cyclosporine A
CSS	coronary stent system
CVA	cerebrovascular accident (or stroke)
DES	drug eluting stent
DLPLA	poly (DL-lactide)
DSMB	Data Safety Monitoring Board
EC	Ethics Committee (EU)
ECG	Electrocardiogram
eCRF	electronic CRF
EECS	everolimus eluting coronary stent
EECSS	everolimus eluting coronary stent system
EQ-5D	Euro-QoL 5D
FDA	Food and Drug Administration
F/U	follow up (verb); follow-up (noun, adjective)
GAD-7	Generalized Anxiety Disorder scale
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GI	gastrointestinal
$HbA1_C$	glycosylated hemoglobin

Acronym or Abbreviation	Complete Phrase or Definition
HCT	hematocrit
ICF	Informed Consent Form
ID	ischemia-driven
IFU	Instructions for Use
IRB	Institutional Review Board (US and Japan)
ITT	Intent-to-Treat
IVRS	interactive voice response service
IVUS	intravascular ultrasound
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
LL	late loss
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
MEC	Medical Ethics Committee (EU)
µg	microgram
Mg	milligram
MI	myocardial infarction
mL	milliliter
ML	MULTI-LINK
MLD	minimum lumen diameter
MLA	mean lumen area
mm	millimeter
N	sample size; also *N*
NIH	neointimal hyperplasia
NQMI	non-Q wave myocardial infarction
OUS	Outside United States
PCI	percutaneous coronary intervention
PK	pharmacokinetics
PLA	poly lactic acid
PLLA	poly (L-lactide)
PMA	pre-marketing approval
PTCA	percutaneous transluminal coronary angioplasty
PTE	per treatment evaluable
PRO	patient reported outcomes
QCA	quantitative coronary angiography
QOL	quality of life
RBC	red blood cell

Acronym or Abbreviation	Complete Phrase or Definition
RC	Research Coordinator
RCA	right coronary artery
RCT	randomized controlled trial
RDS	Rose Dyspnea Scale
RVD	reference vessel diameter
RX	Rapid Exchange
SAE	serious adverse event
SAP	statically analysis plan
SAQ	Seattle Angina Questionnaire
SMC	smooth muscle cell
TIA	transient ischemic attack
TGA	Therapeutic Goods Administration
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularization
TVF	target vessel failure
TVR	target vessel revascularization
UADE	unanticipated adverse device effect
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VO	volume obstruction

APPENDIX II: DEFINITIONS

CLINICAL ENDPOINT DEFINITIONS

DEATH (Per ARC Circulation 2007; 115: 2344-2351)

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

Cardiac death (CD):

Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment.

Vascular death:

Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death:

Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

MYOCARDIAL INFARCTION (MI)

Protocol MI Definition

Classification	Biomarker Criteria	Additional Criteria
Periprocedural PCI	CK-MB > 5 x ULN	Baseline value* < ULN; see also **
Periprocedural CABG	CK-MB > 10 x ULN	Baseline value* < ULN; see also **
Spontaneous	Troponin >ULN or CK-MB > ULN	One or more of the following must also be present: - Symptoms of ischemia; - ECG changes indicative of new ischemia - (new ST-T changes or new LBBB), - Development of pathological Q waves; - Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality
Reinfarction (not related to a procedure)	If the Troponin or CKMB values are stable or decreasing on 2 consecutive samples > 6 hours, a 20% or greater increase 3 to 12 hours after second sample is required to diagnose recurrent MI.	If biomarkers are increasing or peak not reached then insufficient data to diagnose recurrent MI. In this case at least two of the following three conditions must be present: - ECG changes indicative of new ischemia - (new ST-T changes or new LBBB), - Development of pathological Q waves - Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality

ULN=Upper limits of the local laboratory normal (will be collected from each hospital laboratory prior to study commencement);
LBBB=Left Bundle-branch Block
* Baseline CKMB value is required before study procedure and presumes a typical rise and fall post procedure to diagnose a peri procedure MI
** Whenever at least one baseline and one post procedure CK-MB measure are available, adjudication of MI will be based solely on these biomarker values. If the patient has stable ischemic heart disease and the baseline CK-MB measure are not available, they will be assumed to be within normal limits and MI will be adjudicated by the CEC solely according to the post procedure CK-MB measures. TROPONINS WILL NOT BE USED TO DIAGNOSE PERI-PROCEDURAL MI.
If the patient had an elevated CK-MB at baseline (protocol violation), and/or no post procedure CK-MB measures are available (protocol violation), adjudication of a post procedure MI will be based on presence of two of the following three:
1) New ST elevation or ST depression ≥0.1mV in ≥2 contiguous leads on ECG ≥30 min. and ≤48 hrs. post-PCI (Note: ST elevation should be measured at the J point, and ST depression must be horizontal or down-sloping), Or New pathological Q-waves in ≥2 contiguous leads, or new LBBB;
2) Post procedure TIMI 0/1 flow in a coronary artery or a side branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline (core laboratory assessed);
3) Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.

Note: Patients with stable coronary artery disease syndromes may have the baseline CKMB drawn from the arterial sheath during the PCI procedure. If this value is elevated (expected in 1-2% of patients with stable CAD, a post-PCI MI will be diagnosed if the post-procedure CK-MB shows a 20% or greater CK-MB increase on the second sample drawn 3 to 12 hours post procedure (meeting the threshold of CKMB > 5 x ULN), and at least 1 of the following are present:
1) ECG changes indicative of new ischemia - (new ST-T changes or new LBBB),
2) Development of pathological Q waves;
3) Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.
In the absence of any of the above evidence, a > 50% increase in CK-MB over the baseline value, meeting the threshold of CKMB > 5 x ULN, will also qualify for a periprocedural MI.

- **Periprocedural MI After PCI:**

  The periprocedural period includes the first 48 hours after PCI.

- **Periprocedural MI After CABG:**

  The periprocedural period includes the first 48 hours after coronary artery bypass grafting (CABG).

- **Spontaneous MI:**

  MI after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of ECG and angiography supports adjudication to either a target or non-target vessel in most cases.

  With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short and long-term prognosis, a more sensitive definition than for periprocedural MI of any elevation of troponin or CKMB above the 99th percentile of the upper range limit (or ULN if URL is not available) is used. All late events that are not associated with a revascularization procedure will be considered simply as spontaneous.

Myocardial infarctions will also be adjudicated based on the following classification:

- **Q wave MI**

  Development of new, pathological Q wave on the ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads)

- **Non-Q wave MI**

  Those MIs which are not Q-wave MI.

Myocardial infarctions will also be adjudicated as to their relation to the Target Vessel

All infarcts that cannot be clearly attributed to a vessel other than the target vessel will be considered related to the target vessel.

Universal Myocardial Infarction Definition. As a secondary analysis, MI will be adjudicated according to the 2012 Universal Definition**.** Thygesen K et al. Eur Heart J. August 24, 2012

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for 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 ischaemia.
  - 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.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>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. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (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). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Modified World Health Organization (WHO) MI Definition. As a secondary analysis, MI will be adjudicated according to the modified WHO MI definition.

- **Q wave MI**

  Development of new, pathological Q wave on the ECG

- **Non-Q wave MI**

  - Elevation of CK levels to ≥ **two** times the upper limit of normal (ULN) with elevated CK-MB in the absence of new pathological Q waves

  - Non-Q wave MI definition will be used for both peri-procedural MI definition (≤ 48 hours post-procedure) and spontaneous (> 48 hours post-procedure).

REVASCULARIZATION (Per ARC Circulation 2007; 115: 2344-2351)

Target Lesion Revascularization (TLR)

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as ischemia driven or not ischemia driven by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Target Vessel Revascularization (TVR)

TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself. The above two definitions will be used in this protocol.

The above two definitions will be used for CEC adjudication.

Non Target Lesion Revascularization (Non-TLR)

Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

Non Target Vessel Revascularization (Non-TVR)

Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Non-Treated Vessel

Vessel not treated at the time of the index procedure.

Non-Treated Vessel Revascularization

Revascularization of the non-treated vessel.

Ischemia Driven [ID] Revascularization (TLR/TVR)

A revascularization is considered ischemia driven if associated with any of the following:

- Positive functional ischemia study including positive FFR
- Ischemic symptoms and angiographic diameter stenosis ≥ 50% by core laboratory QCA
- Angiographic diameter stenosis ≥ 70% by core laboratory QCA without angina or positive functional study

CORONARY ARTERY BYPASS GRAFT SURGERY [CABG]

Acute CABG is defined as immediate transfer from the cath lab to the operative room for emergent bypass surgery during the initial treatment phase.

CABG during follow-up is only considered as a Clinical-indicated Target Lesion Revascularization if coronary angiography indicates a diameter of stenosis greater than 50% of the stented coronary segment (core lab QCA assessment) associated with one of the following conditions:

- A positive history of recurrent angina pectoris presumably related to the target vessel.
- Objective signs of ischemia (12-lead ECG, exercise test or equivalent) presumably related to the target vessel,
- Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).
- A TLR/TVR with a diameter stenosis ≥70% (core lab QCA assessment) in the absence of the above mentioned ischemic signs or symptoms.

STENT THROMBOSIS (Per ARC Circulation 2007; 115: 2344-2351)

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 guiding catheter has been removed and the subject left the Catheterization lab.

Timing:

Acute stent thrombosis*: 0 - 24 hours post stent implantation

Subacute stent thrombosis*: >24 hours . 30 days post stent implantation

Late stent thrombosis†: 30 days - 1 year post stent implantation

Very late stent thrombosis†: >1 year post stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 - 30 days) - this definition is currently used in the community.

† Including “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target segment revascularization.

Categories (Definite, Probable, and Possible):

Definite stent thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Angiographic confirmation of stent thrombosis*

The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
- Nonocclusive thrombosis
    - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or 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
    - TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

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

† Intracoronary thrombus.

Probable stent thrombosis

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

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

‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

Possible stent thrombosis

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

For the present study the principal definition of stent thrombosis will be ARC definite or probable stent thrombosis.

ANGIOGRAPHIC ENDPOINT DEFINITIONS

ANGIOGRAPHIC BINARY RESTENOSIS (ABR)

Re-narrowing of the artery defined as %DS ≥ 50%.

ACC/AHA Classification Scheme of Coronary Lesions: Lesion-Specific Characteristics

Type A Lesions (High Success, >85%; Low Risk)	
• Discrete (< 10 mm length)	• Little or no calcification
• Concentric	• Less than totally occlusive
• Readily accessible	• Not ostial in location
• Nonangulated segment, < 45°	• No major branch involvement
• Smooth contour	• Absence of thrombus
Type B Lesions* (Moderate Success, 60-85%; Moderate risk)	
• Tubular (10-20 mm length)	• Moderate-to-heavy calcification
• Eccentric	• Total occlusions < 3 mo old
• Moderate tortuosity of proximal segment	• Ostial in location
• Moderately angulated segment, > 45°, < 90°	• Bifurcation lesions requiring double guide wires
• Irregular contour	• Some thrombus present
* Type B1 lesions: One adverse characteristic * Type B2 lesions: ≥ two adverse characteristics	
Type C Lesions (Low Success, <60%; High Risk)	
• Diffuse (> 2 cm length)	• Total occlusions > 3 mo old
• Excessive tortuosity of proximal segment	• Inability to protect major side branches
• Extremely angulated segments > 90°	• Degenerated vein grafts with friable lesions

CHRONIC OCCLUSION

Total Occlusion:

An occlusion with no antegrade filling of contrast to the distal segment (TIMI grade 0)

Sub-total Occlusion:

TIMI grade 1, and with collateral filling of the distal segment

MAXIMUM DIAMETER (Dmax)

Dmax refers to maximum lumen diameter evaluated after pre-dilatation within the boundaries of intended scaffold segment.

IN-STENT

Within the margins of the stent.

IN-SCAFFOLD

Within the margins of the scaffold.

IN-SEGMENT

Within the margins of the stent or scaffold and 5 mm proximal and 5 mm distal to the stent or scaffold.

LATE LOSS (LL)

General definition: Calculated as MLD post-procedure – MLD at follow-up

- In-segment Late Loss: in-segment MLD post-procedure – in segment MLD at follow-up
- Proximal Late Loss: proximal MLD post-procedure – proximal MLD at follow-up (proximal defined as within 5 mm of healthy tissue proximal to the device placement)
- Distal Late Loss: distal MLD post-procedure – distal MLD at follow-up (distal defined as within 5 mm of healthy tissue distal to the device placement)
- In-device Late Loss: in-device MLD post-procedure – in-device MLD at follow-up

PERCENT DIAMETER STENOSIS [%DS]

The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QCA.

REFERENCE VESSEL DIAMETER [RVD]

Average diameter of proximal and distal healthy segments by QCA. 10 mm "normal" reference segments are selected proximal and distal to the stenosis and averaged to define the reference vessel diameter (User defined method). A computer-defined interpolated normal segment will be used to calculate percent diameter stenosis.

RESTENOSIS

Re-narrowing of the artery following the removal or reduction of a previous narrowing.

TIMI (THROMBOSIS IN MYOCARDIAL INFARCTION) FLOW GRADES

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast

material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

ACUTE SUCCESS DEFINITIONS

Clinical Device Success (Lesion Basis)

Successful delivery and deployment of the study scaffold/stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/stent residual stenosis of less than 30% by QCA (by visual estimation if QCA unavailable). When bailout scaffold/stent is used, the success or failure of the bailout scaffold/stent delivery and deployment is not one of the criteria for device success.

Clinical Procedure Success (Patient Basis)

Achievement of final in-scaffold/stent residual stenosis of less than 30% by QCA (by visual estimation if QCA unavailable) with successful delivery and deployment of at least one study scaffold/stent at the intended target lesion and successful withdrawal of the delivery system for all target lesions without the occurrence of cardiac death, target vessel MI or repeat TLR during the hospital stay (maximum of 7 days). In dual target lesion setting both lesions must meet clinical procedure success criteria to have a patient level procedure success.

	Successful Deployment	**No Device Deficiencies**	**QCA requirement**	**In-hospital AE**
Device Success	Yes*	Yes	In-stent %DS < 30%	Not applicable
Procedure Success**	Yes	Yes	In-segment %DS < 30%	No TLF

* Deployment success with any device is a condition of device success, as "can't cross the lesion" is regarded as device deficiencies
** Patient basis. If a patient has multiple lesions, all the lesions must satisfy the success criteria.

DEVICE DEFICIENCY [ISO14155 3.15]

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance ISO14155 3.15

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

ADVERSE EVENT DEFINITIONS

General Definition

ADVERSE EVENT [AE]

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

Unanticipated serious adverse device effect (USADE) refers to any 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 (BS EN ISO 14155:2011).

SERIOUS ADVERSE EVENT [SAE]

If the adverse event meets any of the criteria below, it is regarded as serious adverse event (SAE).

a. led to death,

b. led to serious deterioration in the health of the subject, that either resulted in

   1. a life-threatening illness or injury, or

   2. a permanent impairment of a body structure or a body function, or

   3. in-patient or prolonged hospitalization, or

   4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c. led to fetal distress, fetal death or a congenital abnormality or birth defect

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

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or IFU, that is identified or worsens or occurs in frequency that is not considered normal during a clinical trial.

ADVERSE DEVICE EFFECT

An adverse device effect is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the IFU, device deployment, and user error.

SERIOUS ADVERSE DEVICE EFFECT

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

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).

SPECIFIC EVENT DEFINITIONS (ALPHABETIC ORDER)

ANGINA PECTORIS

Braunwald Classification of Unstable Angina:

I. New onset of severe or accelerated angina. Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

II. Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

III. Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society [CCS] Classification of Stable Angina:

I. Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

II. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

III. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

IV. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

CEREBROVASCULAR ACCIDENT/STROKE

Stroke is defined as a sudden onset of focal neurological deficits due to vascular lesions of the brain that persists >24 hours. Any neurological symptom that lasts < 24 hours is classified as TIA. Stroke results from either of two types of cerebral vascular disturbance: ischemia or hemorrhage.

DISCONTINUITY

Use when geometry of an implanted Absorb BVS has perceived or observed discontinuities (such as gaps, breaks or misalignment) on or after (≥) 6 months post-procedure. Expected by design due to resorption process.

Fracture

When break is suspected to have occurred or reported during use or prior to (<) 6 months post-procedure (whichever is earliest)

DISSECTION

- **National Heart, Lung, and Blood Institute [NHLBI] Dissection Classification System:**

    A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.

    B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.

    C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.

    D. Spiral luminal filling defects.

    E. New persistent filling defects.

    F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

VASCULAR COMPLICATIONS (Am Heart J 2003; 145: 1022-9)

Access site injury requiring invasive treatment associated with protocol required procedures and unscheduled cardiac catheterizations. A vascular complication may include access site hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia or nerve injury.

OTHER PROTOCOL SPECIFIC DEFINITIONS

ANGINA

The first adverse event resulting in the site diagnosis of angina.

ASSIGNED DEVICE

In ABSORB III the assigned device for subjects in the Lead-In group is the investigational device Absorb BVS. For subjects in the randomized portion of ABSORB III (including the Imaging Cohort), the assigned device will be either the investigational Absorb BVS or the FDA approved XIENCE V, based on a 2:1 randomization.

BLEEDING CLASSIFICATION

Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)

Major Bleeding endpoint will be defined by the GUSTO classification of "Severe" or "Moderate" as defined 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 or 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 complications will be site reported.

CHRONIC CONCOMITANT MEDICATIONS

Chronic concomitant medication refers to the following:

a) medication that has been prescribed or is over the counter, that has been taken or will continue to be taken regularly for at least a period of 3 months; or

b) medication that is required to be taken indefinitely by the patient; or

c) medication that has been prescribed or taken multiple times (each time for at least 3 months).

ENROLLED SUBJECT

Subject has signed the Informed Consent.

DWELL TIME

Start date and time the device was inserted into the sheath. Start date and time the device was deployed.

Family History of Coronary Artery Disease (CAD)

Family history of CAD is defined as CAD occurring in male 1st degree relatives (father, brothers) < 55 years old, and female 1st degree relatives (mother, sisters) < 65 years old.

INTENT TO TREAT [ITT] POPULATION

The ITT population is defined as the subjects registered in the study at the point of randomization.

LEGAL AUTHORIZED REPRESENTATIVE

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. (21 CFR Part 50.3)

MAJOR EPICARDIAL VESSELS

- Left anterior descending artery [LAD] with septal and diagonal branches;
- Left circumflex artery [LCX] with obtuse marginal and/or ramus intermedius branches;
- Right coronary artery [RCA] and any of its branches.

NO-REFLOW

An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.

PERCUTANEOUS CORONARY INTERVENTION [PCI]

Refers to all interventional cardiology methods for treatment of coronary artery disease.

PRINCIPAL INVESTIGATOR

A physician-specialist, related to the study, who is responsible for the overall conduct of the trial at all sites and compliance with protocol and relevant.

PRIMARY INVESTIGATOR

A physician responsible for conducting the clinical trial at each investigational site.

PROCEDURE START DATE AND TIME

Procedure start date and time is recorded as the date and time the first guiding catheter was inserted into the subject.

PROCEDURE END DATE AND TIME

Procedure end date and time is recorded as the time the last guiding catheter was removed from the subject.

SUCCESSFUL PRE-DILATATION

Pre-dilatation has been successfully completed without complications if all of the following apply:

- For randomized subjects: RVD remains ≥ 2.50 mm - ≤ 3.75 mm and length of the lesion that will be covered by the device (including any edge dissections) is still ≤ 24 mm
- For Lead-In subjects: RVD remains ≥ 2.75 mm - ≤ 3.25 mm and length of the lesion that will be covered by the device (including any edge dissections) is still ≥ 8 mm - ≤ 14 mm
- Residual %DS is a maximum of < 40% (per visual estimation), ≤ 20% is strongly recommended.
- TIMI Grade-3 flow (per visual estimation),
- No angiographic complications (e.g. distal embolization, side branch closure),
- No dissections NHLBI grade D-F
- No chest pain lasting > 5 minutes
- No ST depression or elevation lasting > 5 minutes.

TARGET LESION (Analysis Definition)

The target lesion is defined as the lesion that has met the angiographic inclusion and exclusion criteria in a registered subject upon calling IVRS.

Under these conditions, the lesion will be considered the target lesion regardless of the device implantation and treatment actually received.

TARGET VESSEL

The entire epicardial vessel in which the target lesion is located.

RANDOMIZED SUBJECT

Subject is considered randomized after the interactive voice response system (IVRS) has been called and a device (Absorb BVS or XIENCE) has been assigned.

REGISTERED SUBJECT

Subject is considered registered upon randomization. Lead-In subjects will be considered registered upon calling IVRS.

UNSTABLE CARDIAC ARRYTHMIA

Any irregularity in the heart's natural rhythm associated with hemodynamic instability that has not been controlled in spite of treatment.

APPENDIX III: SCHEDULE OF EVENTS

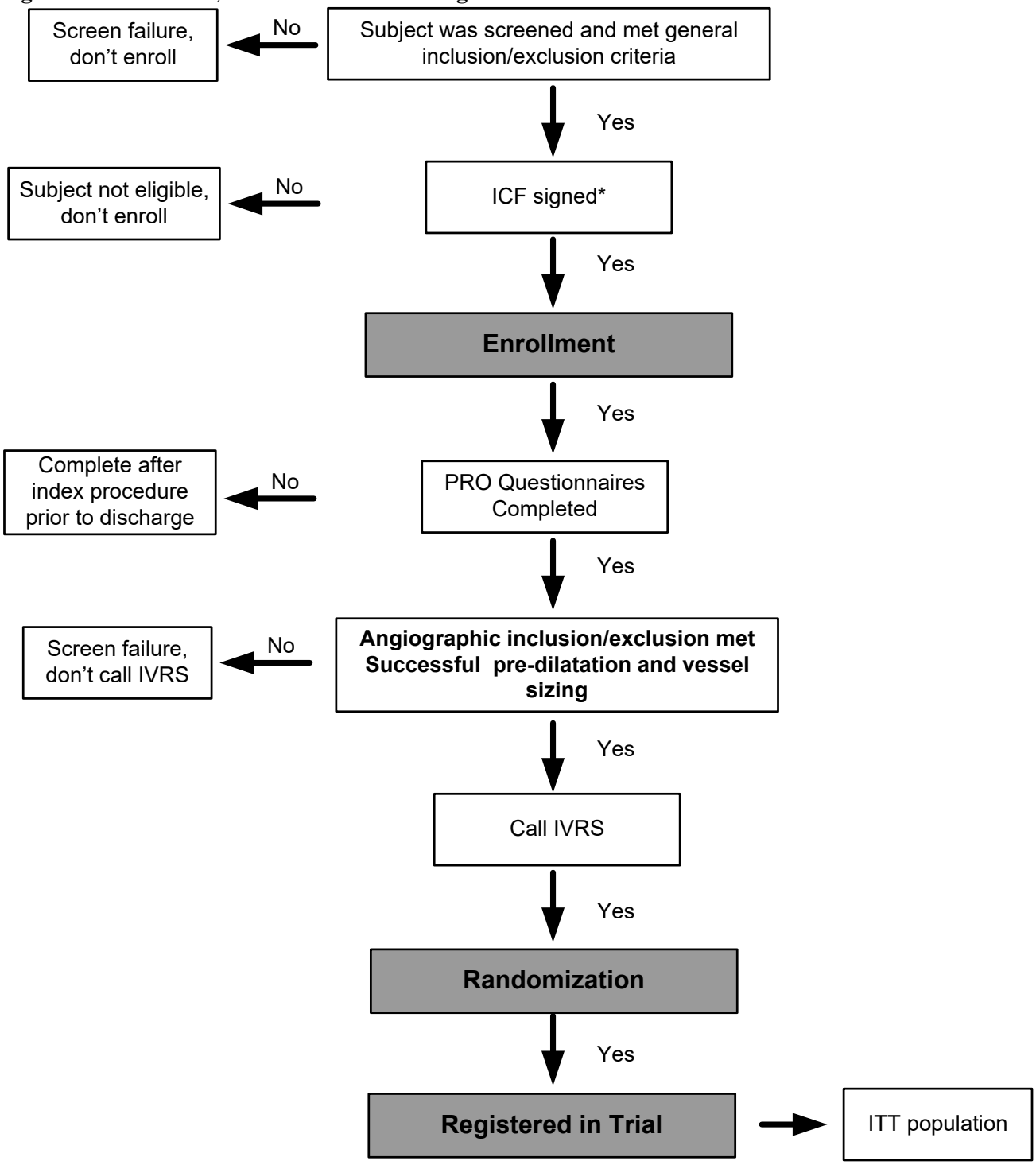
PROCEDURE/TEST	Baseline	Baseline (within 7 days)	Pre-Procedure (within 24 hours)	Procedure	Post-Procedure	30 days (± 7 d) Telephone contact or office visit	180 days (± 28 d) Telephone contact or office visit	1 yr (± 28 d) office visit	2, 3, 4, 5 yrs (± 28 d) Telephone contact or office visit	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors, Angina Status, Cardiac History)	✓									
Subject Informed Consent (Must be obtained prior to any study related testing or procedures)	✓									
General Inclusion/Exclusion Criteria	✓									
Angiographic Inclusion/Exclusion Criteria				✓[7]						
Pregnancy Test (if applicable)		✓								
Hgb, Platelet Count, Creatinine, HbA1c, eGFR, WBC	✓[1]									
CK and CK-MB			✓[2]		✓[3]					✓[6]
Troponin I or T										✓[6]
ECG			✓[2]		✓[4]			✓	✓[8]	✓[6]
Coronary Angiogram, IVUS or OCT				✓[7]					✓[8]	
Study device information				✓						
Per Protocol Medications[5]			✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓			✓	✓	✓	✓	✓	✓	✓
Adverse Events				✓	✓	✓	✓	✓	✓	✓
Patient Reported Outcome Instruments[9]	✓[10]					✓		✓	✓[11]	

1. The 21 day labs should be known prior to index procedure. HbA1c is to be collected in diabetic subjects only, and its result is not needed prior to the index procedure.
2. Within 48 hours pre-procedure will be acceptable except when there is evidence of acute or recent (<7 days) myocardial infarction or unstable angina prior to the procedure, in which case pre-procedure draws/assessments must be within 24 hours. For ECGs, 12-lead must be used. If the subject does not have a known diagnosis of AMI or unstable angina within 96 hours prior to the index procedure, assessment of cardiac enzymes may be obtained after the start of the index procedure but prior to device implantation.
3. Three draws required: 1) Pre-procedure (prior to stent deployment); 2) 6 -12 hours post-procedure; 3) 18-24 hours post-procedure or at the time of discharge as long as discharge is at or after 16 hours post-procedure (for hospitals required to discharge stable subjects prior to 16 hours, the subject may be discharged but will have to return to the enrolling institution for their second biomarker draw). If either of the post-procedure CK-MB levels are ≥ 3 x ULN, serial CK and CK-MB levels must be drawn until they are falling.
4. ECG must be done between 30-90 minutes post-index procedure.
5. Prasugrel 5 or 10 mg daily, clopidogrel a minimum of 75 mg daily or ticagrelor 90 mg twice daily, must be given for a minimum of 12 months, and Aspirin ≥ 75 mg to ≤ 100 mg daily must be taken through 5 years follow up during the study, and should continue to be taken indefinitely. If a subject develops hypersensitivity to clopidogrel, prasugrel or ticagrelor, subject may be switched to ticlopidine at a dose in accordance with standard hospital practice.
6. Cardiac enzymes CK and CKMB must be collected and ECG must be done. Troponin measurement is per site standard.
7. Baseline (prior to pre-dilatation) and final (after stenting/post dilatation) angiogram must be obtained and sent to the core laboratory. For imaging sites enrolling an imaging subject, if vessel sizing is conducted using IVUS, OCT or on-line QCA, these images must also be sent to their respective core laboratory. For subjects in imaging study group, post-implantation angiogram and IVUS, or angiogram and OCT will be conducted and images sent to their respective core laboratory. Images will be sent to respective core laboratory.
8. Subjects in the imaging study group will receive either at 3 years an angiogram, ECG, plus IVUS or OCT.
9. Patient Reported Outcome instruments (EQ-5D, SAQ, RDS, GAD-7) will be administered to the 2000 primary analysis subjects in ABSORB III only
10. Every effort should be made to have subjects complete all four patient reported outcomes questionnaires prior to the procedure. However, in situations where this is absolutely not possible, subjects may complete them post-procedure, prior to discharge. Subjects who complete their questionnaires post-procedure should base their responses on their condition prior to the procedure.

EQ-5D, SAQ, RDS, GAD-7 will be administered through 3 years; only EQ-5D and SAQ will be administered at 5 years

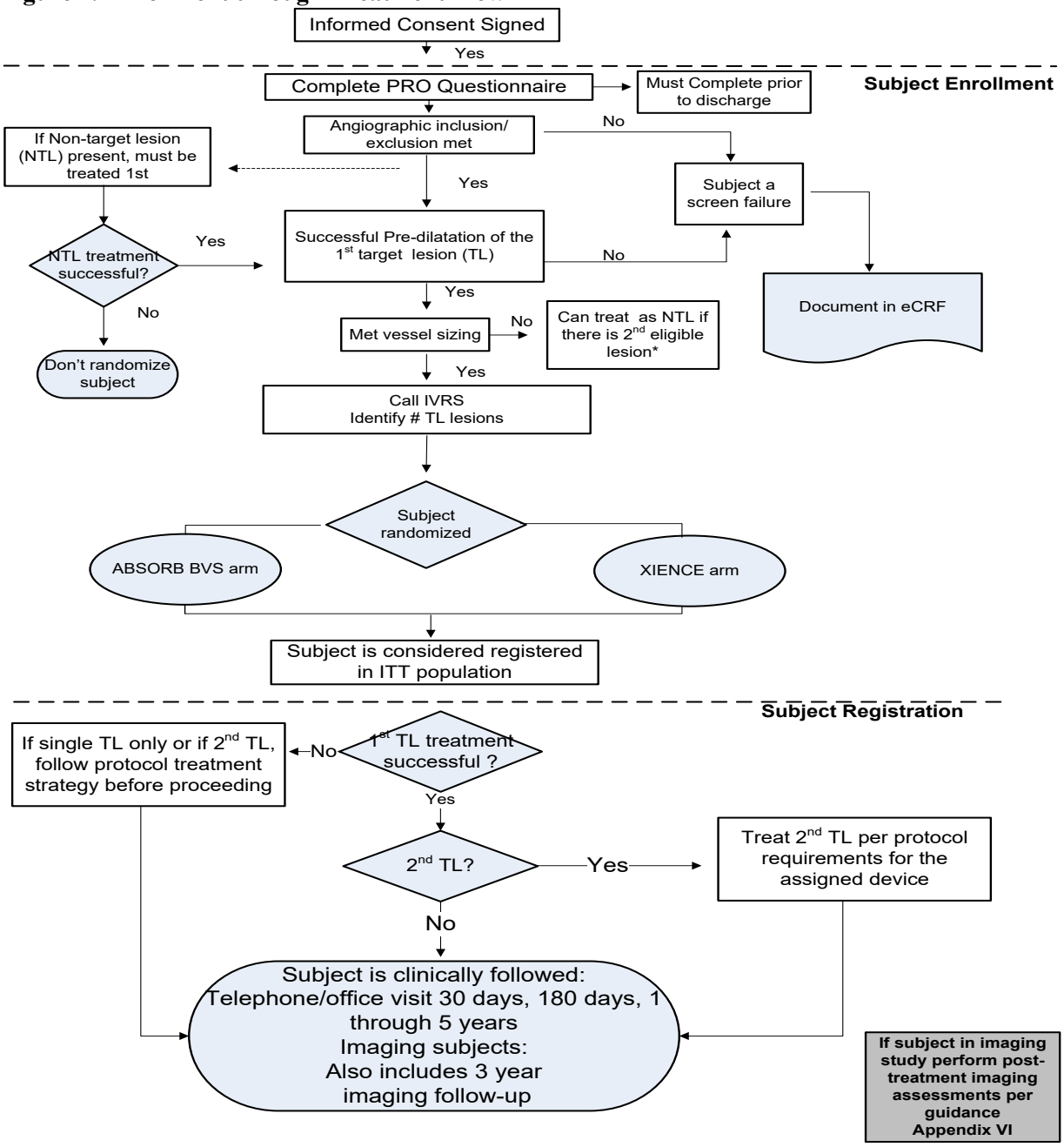
APPENDIX IV: ENROLLMENT AND REGISTRATION PROCESS

Figure 1. Enrollment, Randomization and Registration



[1]Lead-In subjects will be randomized and will be considered registered in the trial upon calling IVRS.
* The ICF can be signed before or after the general inclusion criteria screening. Once signed, a subject is considered enrolled.

Figure 2. Enrollment through Treatment Flow



Note:

* If there are two lesions and vessel sizing of the intended 1st target lesion fails, this lesion can be treated as a non-target lesion and the second lesion can be treated as the 1st target lesion, only after meeting the pre-dilatation and vessel sizing criteria. If a single intended target lesion and vessel sizing criteria not met, then subject cannot be registered in trial.

For the Lead-In subjects, randomization is substituted by subject ID assignment.

The ICF can be signed before or after the general inclusion criteria screening. Once signed, a subject is considered enrolled.

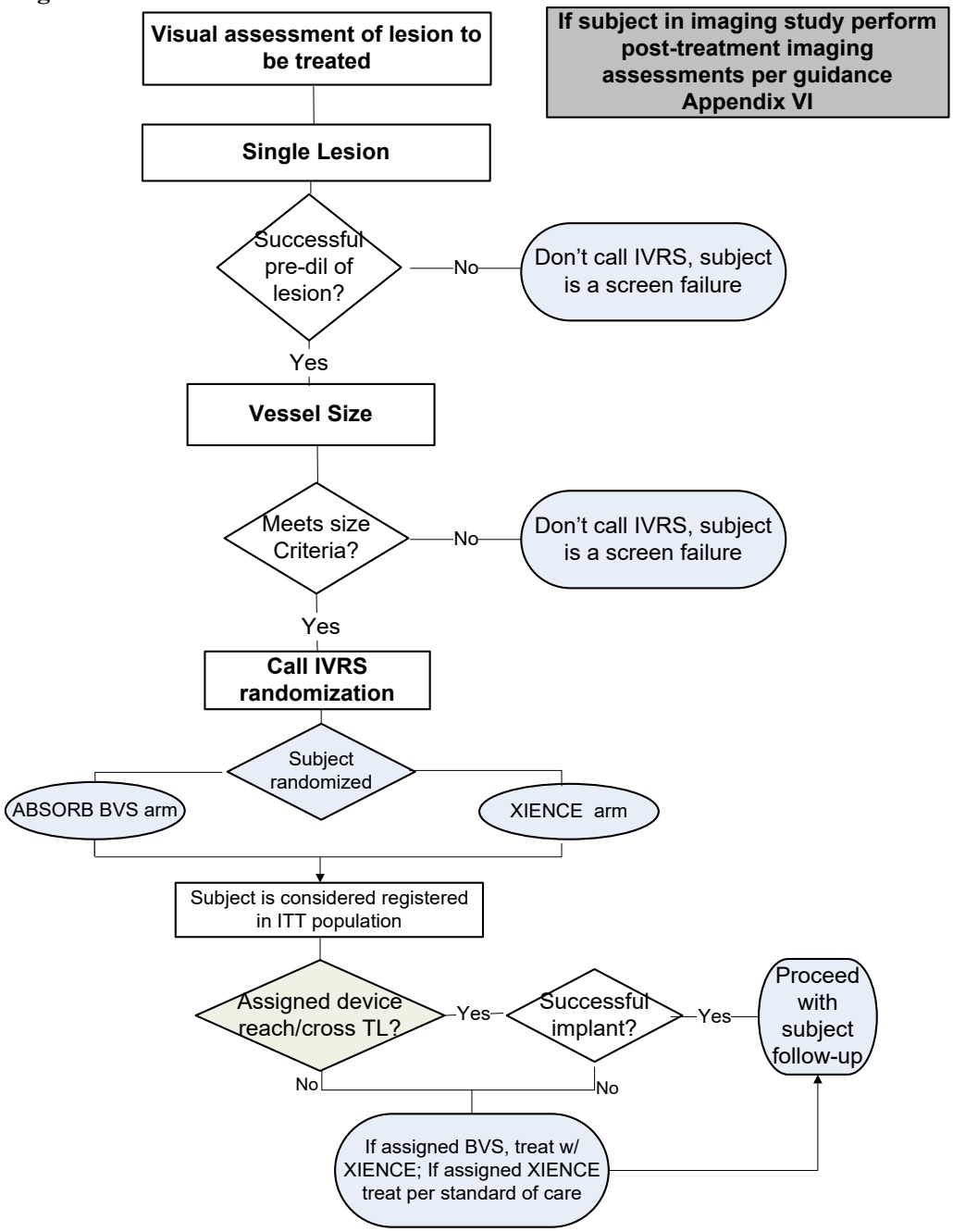
If two target lesions, the same vessel sizing modality and treatment requirements must be used on both target lesions.

Subjects will be clinically followed up to 5 years

Patient Reported Outcomes questionnaires should be completed prior to procedure after signing ICF, but must occur prior to discharge. The PRO questionnaires must be completed at post-procedure, 30 days, 1, 2 and 3 years for all 4 questionnaires and at 5-year follow-up for EQ-5D and SAQ.

APPENDIX V: VESSEL TREATMENT & RANDOMIZATION

Figure 1. Single Vessel Treatment

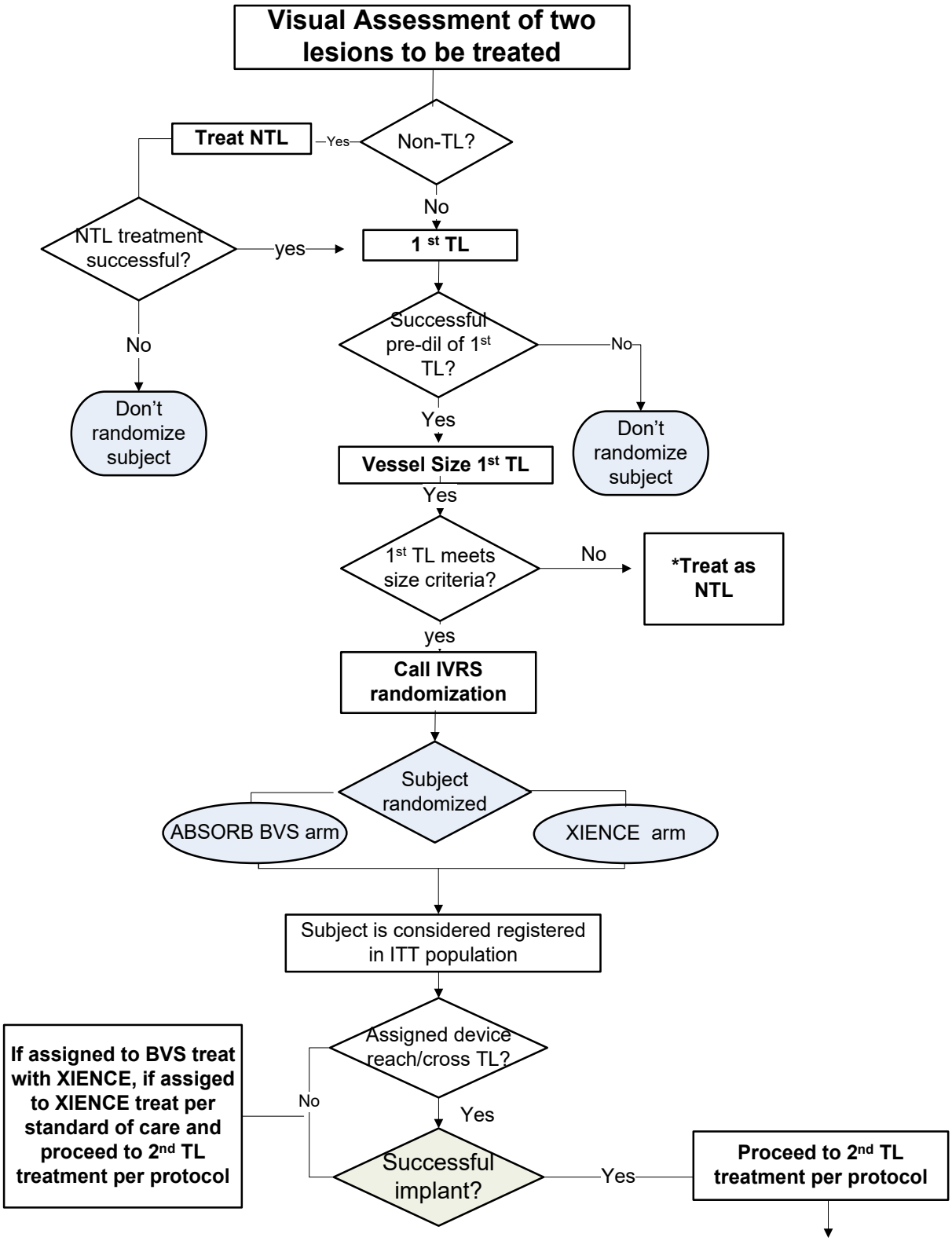


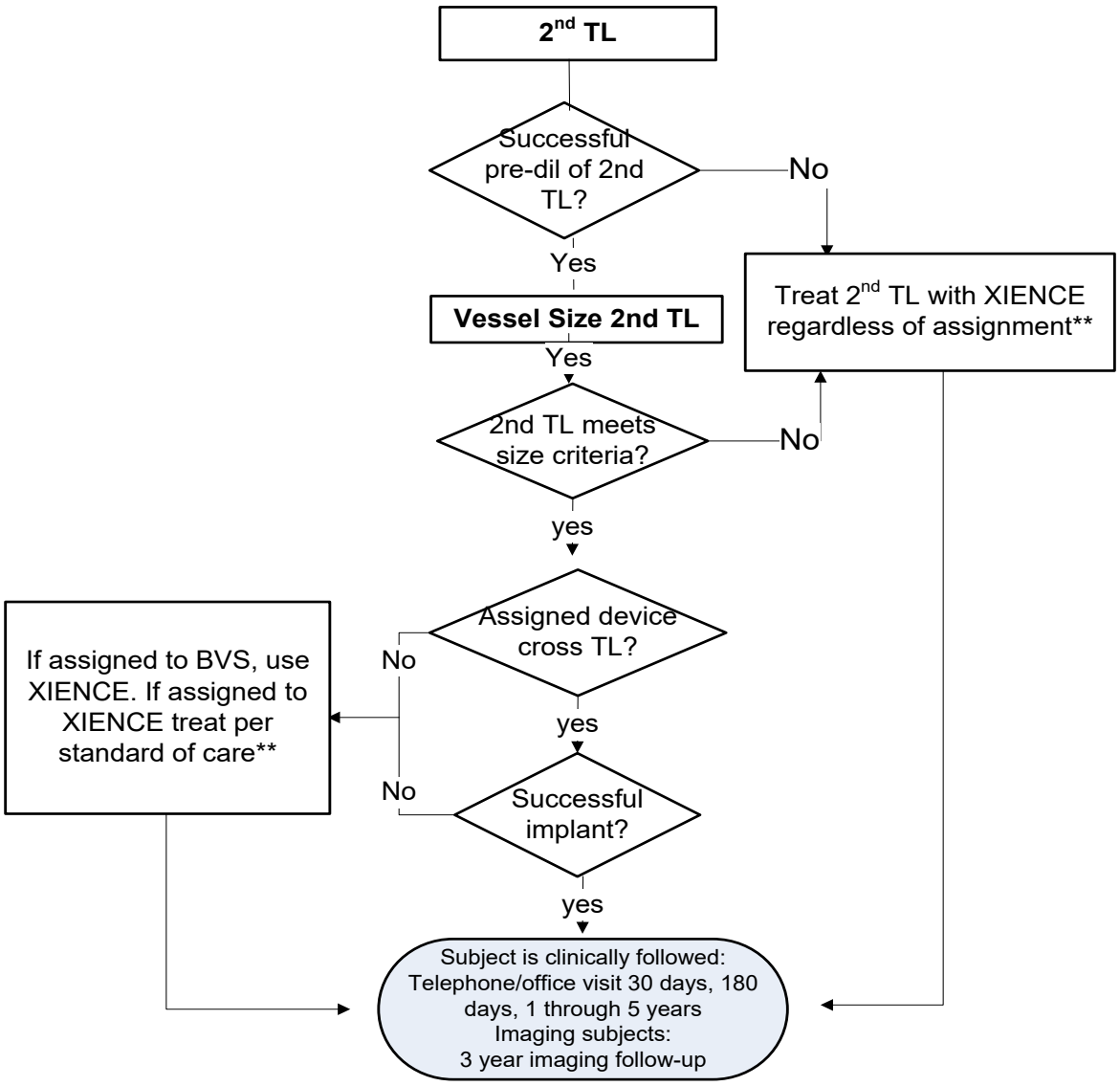
[1] The lesion must be successfully pre-dilated and meet vessel sizing criteria prior to randomizing subject.

Note:

- Due to pre-dilatation being required prior to vessel sizing and randomization, there is the possibility of an "unstable" target lesion. Therefore, time period between pre-dilatation and vessel sizing should be minimized to being as brief as possible.
- For Lead-In subjects randomization is substituted by subject ID assignment.
- Vessel sizing is done by visual estimation.

Figure 2. Vessel Sizing: Two Vessel Treatment[1]



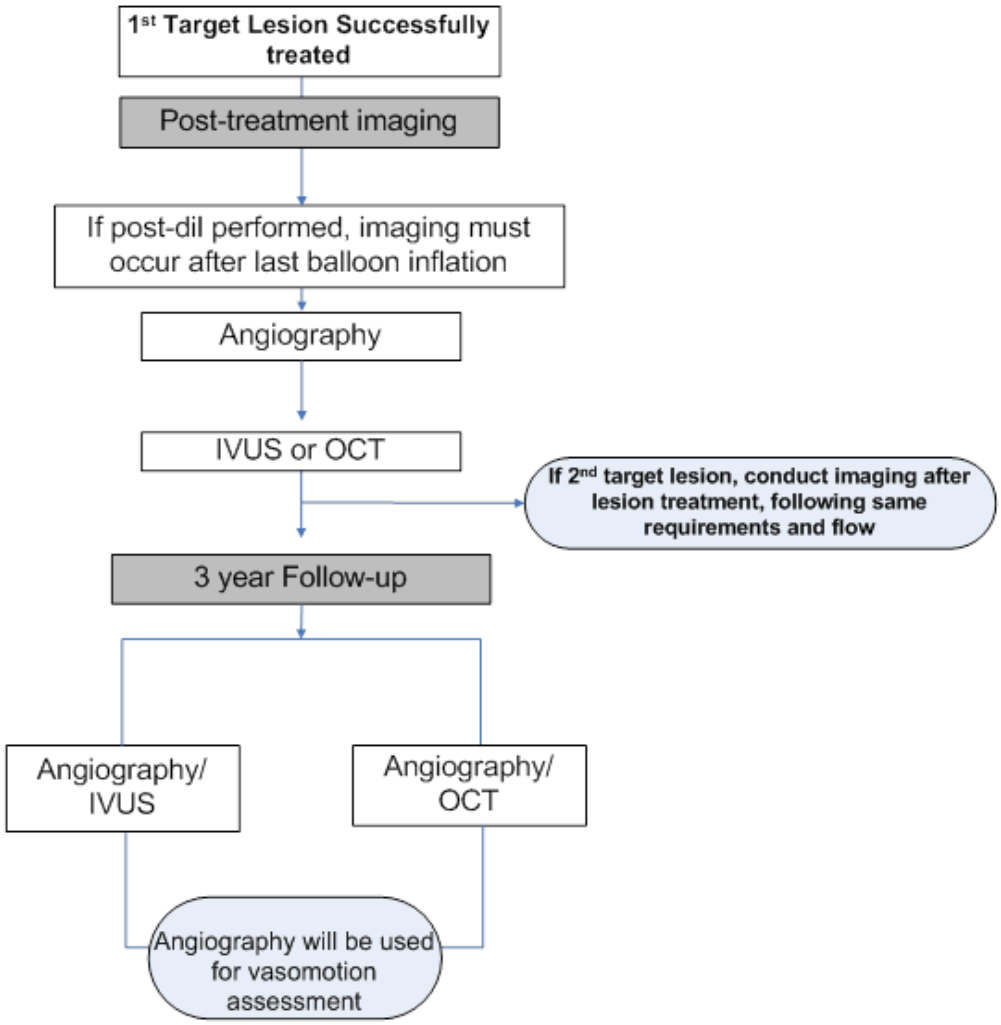


[1] If 1st lesion is a non-target lesion, follow single vessel treatment flow.

Note:

- *If there are two lesions and vessel sizing of the intended 1st target lesion fails, this lesion can be treated as a non-target lesion and the second lesion can be treated as the 1st target lesion, only after meeting the pre-dilatation and vessel sizing criteria. Subject cannot be randomized if the 2nd lesions fail to meet pre-dilatation and sizing criteria.
- **If assigned to BVS and 1st lesion treatment fails with BVS and treatment with XIENCE is unsuccessful, then treatment of the 1st and 2nd lesion is per standard of care.
- Due to pre-dilatation being required prior to vessel sizing and randomization, there is the possibility of an "unstable" target lesion. Therefore, time period between pre-dilatation and vessel sizing should be minimized to being as brief as possible.
- For Lead-In subjects randomization is substituted by subject ID assignment
- Vessel sizing is done by visual estimation.
- In the case of two target lesions assigned to the Absorb BVS and the first lesion is unsuccessfully treated with the Absorb BVS, if the first lesion can be successfully treated with a XIENCE or other stent, the second target lesion should be treated with an Absorb BVS; if the first lesion is unsuccessfully treated with a XIENCE or other stent, the second target lesion should be treated per standard of care (XIENCE stent preferred) but NOT with an Absorb BV, at another session.

APPENDIX VI: IMAGING FLOW AND SCHEDULE



Note:
[1] Use IVUS or OCT depending on what modality available at the site.
Refer to core laboratory guidelines in the Imaging Guidance Document regarding imaging requirements.

APPENDIX VII: EVALUATION OF LEAD-IN PHASE

The ABSORB III Lead-In Phase will begin immediately prior to the randomization phase of the ABSORB III. The main objective of the Lead-In Phase will be the evaluation of the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice. The primary area of learning in the usage of Absorb BVS is in the vessel sizing, lesion preparation, and device delivery and deployment, as these variables reflect the change in practice that occurs with the use of a polymeric scaffold compared to a metallic stent. The Lead-In Phase will involve up to 35 sites and up to 50 subjects treated with Absorb BVS. Each site will be allowed to register 5 subjects. The participating sites will not have had previous experience with Absorb BVS, therefore will be limited to US sites only. As the Absorb physician training will be used to train all physicians in the usage of Absorb BVS, and the Lead-In Phase is intended to evaluate the training program, 35 sites are deemed sufficient.

During the Lead-In phase, there will be four key areas specific to lesion/vessel selection, lesion preparation and device delivery and deployment that will be measured during the time of and following the index procedure. The four variables are as follows:

1. **Angiographic inclusion/exclusion:** At the time of the index procedure all angiographic inclusion/exclusion must be met. Selection of the appropriate target vessel and lesion criteria has been found to be important in the proper delivery and deployment of Absorb BVS. The expected adherence to the angiographic inclusion/exclusion will be set at the success criteria of 95%. The criteria is based on ASBORB EXTEND data in which out of 469 patients, there were 24 angiographic inclusion/exclusion deviations (5% angiographic inclusion/exclusion deviation rate).

2. **Vessel sizing met protocol required criteria:** Retrospective analysis will be completed by the angiographic core laboratory. Appropriate vessel sizing is important in the selection of the correct Absorb BVS diameter. The RVD will be visually assessed by investigators at the time of the index procedure, and will be sent to angiographic core laboratory to assess if vessel sizing was done appropriately. The targeted Dmax [36] range as assessed by the angiographic core laboratory is ≥ 2.5 to ≤ 3.3 mm, with an acceptable range between 2.25 to ≤ 3.3 mm. This criterion is based on ABSORB EXTEND data in which an angiographic core laboratory retrospective analysis conducted on 108 target lesions that were selected by ABSORB EXTEND investigators using on-line QCA (Quantitative Coronary Angiography) [56]. The acceptable range identified above is considered appropriate based on ABSORB EXTEND data in which out of 108 lesions 69.4% of vessels treated with the 3.0x18 mm Absorb BVS fell within the Dmax range of ≥ 2.5 to ≤ 3.3 mm and 26.9% of vessels had a Dmax range < 2.5 mm [56].Furthermore, preliminary analysis from ABSORB Cohort B has demonstrated that the placement of the 3.0 mm Absorb BVS in a vessel < 2.5 mm has not resulted clinical and angiographic differences as compared to vessels > 2.5 mm [57].

3. **Treatment strategy followed per the protocol:** All treatment strategy requirements must be met at the time of the index procedure. Proper delivery and deployment of the Absorb BVS is also dependent on variables such as appropriate guide catheter choice,

[36] Dmax is defined as the maximum lumen diameter of the vessel within the target lesion segment

pre-dilatation strategy, inflation timing and potential post-dilatation strategy. Therefore, the expected adherence to the treatment strategy will be set at the success criteria of 95%. This is based on ABSORB EXTEND data in which there were 32 treatment deviations out of 469 subjects registered in the trial (7% treatment deviation rate).

4. **Device success:** The device success criteria will be based on the protocol definition that is detailed in **Appendix II**. The expected device success will be 90%.

Each of these variables can be evaluated acutely and will provide the sponsor with a measure of adherence to the physician training program. Subject registration will be conducted in 5 sets of 10 subjects. After each subject is registered in the trial, the core laboratory will be review the angiographic data within 3 business days and monitoring of the data will occur within 1-2 business days. After the registration of each subject set, AV will evaluate the four criteria for all 10 subjects to determine whether they met the above criteria. Communication to the sites will be conducted to indicate a short pause in enrollment to evaluate each subject set. If there are deviations to the above criteria, modification to the training plan and retraining of identified elements will be conducted at the sites. Furthermore, AV will communicate to the sites when the continuation of subject enrollment/registration to the sites can occur. Regarding the vessel sizing criteria, after the first missed vessel sizing by an investigator, they will receive immediate feedback from the sponsor and core laboratory, and retraining if needed.

The data for each enrolled subject will be collected through the electronic case report forms (eCRFs). Sites will be required to enter the Lead-In data within 2 business days of the index procedure and data from each subject will be cleaned and evaluated throughout the enrollment of the 50 subjects. Identified trends may require for modification in training or retraining of investigators, which will be implemented immediately. Modifications will not be required of those elements that exceed the criteria set. The randomization phase of the trial will occur upon the enrollment of the 50th patient. Mean outcomes for all 50 subjects on the four variables will be analyzed within 5-7 days of the 50th subject. If the mean outcomes meet the criteria detailed above, randomization will resume immediately. The 50 subjects will receive annual follow-up through 5 years and the sponsor will provide clinical data to the FDA through 5 years.

The outcomes from the lead-in phase will determine whether the physician training requires further modification to meet the needs of the US physicians. The small sample size and small number of sites is appropriate for the intent of assessing quality and sufficiency of the training program before the training is applied to the entire ABSORB III trial. The inclusion of up to 50 subjects is considered sufficient as the physician training has shown to be effectively applied in the ABSORB EXTEND trial, in which over 550 subjects have been enrolled and the ABSORB II trial in which over 99 subjects have been enrolled thus far.

APPENDIX VIII: RISK STRATIFICATION OF CARDIAC CATHETERIZATION, STENTING AND PERCUTANEOUS TRANSCATHETER CORONARY ANGIOPLASTY

Potential risks associated with the study device and everolimus were described in the original protocol. Based on additional clinical and commercial experience, Abbott Vascular has updated the BVS IDE IFU. The below section provides a consolidated list of anticipated adverse events and, in alignment with ISO14155:2011 requirements, the estimated frequencies of those risks.

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures. It is expected that the risks will not be significantly different with the use of the Absorb BVS and XIENCE V stent in this trial. The incidence rates of the known complications that may arise from a stenting procedure were obtained from the pooled XIENCE V trials conducted by AV (Spirit First, Spirit II, Spirit III RCT, Spirit III JPN, Spirit III 4.0 mm, Spirit IV, Spirit V Diabetic, Spirit V Registry, Spirit Women, XV USA, XV DAPT, and XV India using MedDRA Preferred Terms of site-reported 1 year adverse events regardless of relationship to device or procedure) and were classified using the frequency categories as below. Death and stent thrombosis within 1 year have been observed in < 2.0% of the patients enrolled in these trials.

1. Very common: ≥ 10%: Unstable or stable angina pectoris

2. Common: ≥ 1.0% to < 10%: Cardiac, pulmonary or renal failure; access site complications including pain, hematoma, or hemorrhage; vascular complication including at the entry site, which may require vessel repair; coronary artery dissection; arrhythmia including atrial and ventricular; myocardial infarction, including acute myocardial infarction; nausea and vomiting; hypotension; hypertension; restenosis

3. Uncommon: ≥ 0.1% to < 1.0%: Cardiac arrest; emergent or non-emergent surgery; allergic or hypersensitivity reactions to contrast agent or platinum, polymer poly (L-lactide) (PLLA), polymer poly (D,L-lactide) (PDLLA), and drug reactions to everolimus, antiplatelet drugs or contrast agent; bleeding complications which may require transfusion; coronary artery spasm; distal emboli; fever; catheter site infection or pain; myocardial ischemia; palpitations; coronary artery perforation; pericarditis, peripheral ischemia (due to vascular injury); pseudoaneurysm; pulmonary edema; stroke/CVA/TIA; total occlusion of coronary artery; ventricular tachycardia; ventricular fibrillation; vessel dissection

4. Rare: ≥ 0.01% to < 0.1%: Arteriovenous fistula; cardiac tamponade; coronary artery embolism; arterial injury; procedural nausea; shock; peripheral artery dissection; peripheral nerve injury; renal insufficiency; pericardial effusion

5. Very Rare: < 0.01% (including not reported AEs): Abrupt coronary artery closure; coronary artery aneurysm; arterial rupture; everolimus IFU risks.

Some IFU risks, including everolimus risks have not been observed in Abbott Vascular clinical studies. These risks are listed in the very rare category. There may be risks related to the device that are unknown at present. Likewise the exact frequency of the risk might be unknown.

APPENDIX IX: CONTACT INFORMATION

A list of investigational site co-ordinates can be obtained upon request from the Clinical Project Manager for the study. The Clinical Project Manager can be reached at 408-845-3000.

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ADDENDUM A: PHARMACOKINETICS SUB-STUDY SYNOPSIS

PROTOCOL 10-392

ABSORB III RCT
PHARMACOKINETICS (PK) SUB-STUDY SYNOPSYS

Date	August 16, 2018
Sub-Study Co-Primary Investigators	David G. Rizik, MD Scottsdale Healthcare Scottsdale, AZ Louis A. Cannon, MD Cardiac and Vascular Research Center of Northern Michigan Petoskey, MI
Planned Number of Sites and Region(s)	A maximum of 5 sites in the United States
Abbott Vascular Medical Expert	Krishna Sudhir, Divisional Vice President Medical Affairs, Chief Medical Office
Study Type	Prospective, open-label, non-blinded study
Sponsor / Data Monitoring/ Data Management/Data Analysis	Abbott Cardiovascular Systems, Inc. 3200 Lakeside Drive Santa Clara, CA 95054
Study Monitor	Abbott Vascular
Enrollment/Randomization Service	Bracket 303 2nd Street, Suite 700 South San Francisco, CA 94107
Electronic Data Capture Software	Medidata RAVE
Blood Sample Analysis Core Laboratory	Eurofins | ADME Bioanalyses Vergeze, France
Data Analysis Core Laboratory	Kinesis Pharma BV Breda, The Netherlands
Clinical Events Committee	Cardiovascular Research Foundation, New York, NY
Sub-study Author	Maureen Kennedy, MN Senior Manager – Clinical Science

<table>
<tr><td>Study Name</td><td>ABSORB III PK Sub-study: 10-392</td></tr>
<tr><td>Investigational Device</td><td>Absorb™ Bioresorbable Vascular Scaffold (BVS) System:
Scaffold diameters: 2.5, 3.0 and 3.5 mm
Scaffold lengths: 8, 12, 18, and 28 mm</td></tr>
<tr><td>Objective</td><td>To determine the pharmacokinetics of everolimus delivered by the Absorb BVS in a separate and non-randomized cohort of subjects who only receive Absorb BVS with a maximum of two de novo native coronary artery lesions after implantation of the Absorb BVS. (Note: The ABSORB III PK subjects will not contribute to the determination of the ABSORB III RCT primary endpoint.)</td></tr>
<tr><td>Sub-study Design</td><td>A prospective, open-label, non-blinded study enrolling approximately 12 subjects in up to 5 US sites.</td></tr>
<tr><td>Subject Number</td><td>Total number of patients: Approximately 12 (as distributed below)

Table 1: Drug Content in Absorb BVS
<table><tr><th>Absorb BVS Diameter (mm)</th><th>Absorb BVS Length (mm)</th><th>Drug Dose (µg)</th></tr><tr><td>2.5, 3.0</td><td>8</td><td>76</td></tr><tr><td>2.5, 3.0</td><td>12</td><td>114</td></tr><tr><td>2.5, 3.0</td><td>18</td><td>181</td></tr><tr><td>2.5, 3.0</td><td>28</td><td>276</td></tr><tr><td>3.5</td><td>12</td><td>135</td></tr><tr><td>3.5</td><td>18</td><td>197</td></tr><tr><td>3.5</td><td>28</td><td>308</td></tr></table>
Table 2: Treatment Group and Drug Dosage
<table><tr><th>Treatment Groups</th><th>Drug Dose (µg)</th></tr><tr><td>Single Scaffold</td><td>76-308</td></tr><tr><td>≥ 2 Scaffolds[+]</td><td>≥ 152[++]</td></tr><tr><td colspan="2">[+]Two lesions in two separate vessels or bailout
[++]Minimum dosage a subject can receive based on use of two of the smallest scaffold sizes (2.5/3.0 x 8 mm)</td></tr></table>
To ensure the PK measurements reflect everolimus exposure due to Absorb BVS only, the PK sub-study will <u>not</u> allow non-target lesion treatment.

Subjects will be included in the PK analysis only if all intended Absorb BVS are implanted <u>and</u> no other device is used/implanted.</td></tr>
</table>

Blood Sampling Timing	• Pre-Absorb BVS implantation: Baseline
	  • Baseline is defined as prior to implantation of the first Absorb BVS; the blood sample will be drawn on the day of the index procedure either through a heparin lock, venous sheath, or venipuncture.
	• Post-Absorb BVS implantation: 10 and 30 minutes, 1 hr, 2 hrs, 4 hrs, 6 hrs , 12 hrs, 24 hrs (1 day), 48 hrs (2 days), 72 hrs (3 days), 96 hrs (4 days), 120 hrs (5 days), 168 hrs (7 days), 336 hrs (14 days), and 720 hrs (30 days)
	  • Post-implantation blood samples will be drawn at the time intervals stated above; timing of the post-implantation sampling will begin when the last Absorb BVS is deployed, i.e. last Absorb BVS delivery catheter is removed from the body.

Follow-up	• Refer to Section 7.5 *Clinical and Imaging Follow-Up for All Subjects* • Note: Follow-up for PK sub-study subjects will not include administration of the PRO tools nor imaging follow-up.
PK Parameters	• t_{max} • C_{max} • AUC_{0-24h} • AUC_{0-t} • $AUC_{0-\infty}$ • λ_z • $t_{1/2term}$ • CL
Safety Monitoring	Refer to *Section 9.0 Adverse Events*
Subject Enrollment	Unlike the ABSORB III primary analysis group and Imaging cohort, IVRS will not be called for PK subjects until after a) successful pre-dilatation and b) completion of the index procedure.

Exclusion from Analysis and Follow-up	• Subjects in whom an Absorb BVS enters the body but is not implanted will be excluded from the sub-study analysis and will require 30-day safety follow-up. • Subjects in whom an Absorb BVS and a non-Absorb BVS device are implanted will be excluded from the sub-study analysis and will require the full 5-year follow-up as described in Section 7.5 *Clinical and Imaging Follow-Up for All Subjects.* (Note: Completion of the PRO tools and imaging follow-up will not be required.) • In all of the above cases, subjects will be replaced in the PK sub-study.
Inclusion Criteria	**General Inclusion Criteria:** Refer to Section 6.3.1.1 *General Inclusion Criteria* for complete list **Angiographic Inclusion Criteria** 1. One or two *de novo* target lesions: a. If two target lesions are present, they must be present in different epicardial vessels and both must satisfy the angiographic eligibility criteria. b. The definition of epicardial vessels means the LAD, LCX and RCA and their branches. Thus, the patient must not have lesions requiring treatment in e.g. both the LAD and a diagonal branch. 2. Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥ 50% and < 100% with a TIMI flow of ≥ 1 and one of the following: stenosis ≥ 70%, an abnormal functional test (e.g., fractional flow reserve, stress test), unstable angina or post-infarct angina. a. Lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.50 mm and ≤ 3.75 mm. b. Lesion(s) must be located in a native coronary artery with length by visual estimation of ≤ 24 mm.
Exclusion Criteria	**General Exclusion Criteria:** Refer to Section 6.3.1.2. *General Exclusion Criteria for the complete list; the following change/modification applies to criterion #8:*

	8. Subject has undergone prior PCI within the target vessel(s) during the last 12 months. a. Prior PCI to a non-target vessel not using drug-eluting/coated devices (e.g. balloon, stent) is acceptable if performed anytime > 30 days before the index procedure**.** b. Prior PCI to a non-target vessel using drug-eluting/coated devices is acceptable if performed >6 months before the index procedure. c. Peripheral interventions not using drug-eluting/coated devices are acceptable if performed anytime > 30 days before the index procedure or between 24 hours and 30 days before the index procedure if successful, uncomplicated. d. Peripheral interventions using drug-eluting/coated devices are acceptable if performed > 6 months before the index procedure. **Angiographic Exclusion Criteria:** Refer to Section 6.3.2.2 *Angiographic Exclusion Criteria for the complete list*
Lesion Selection	Refer to Section 4.4 *ABSORB III Treatment Flow and Lesion Selection (Please note again that non-target lesion treatment is not allowed in the PK sub-study.)*
Treatment Strategy	Refer to Section *7.3.4 Treatment Rules of the Target Lesion(s) with the following exceptions:* • In the PK sub-study, all target lesions are to be treated with the Absorb BVS only • Subjects in the PK sub-study will not be randomized; any references to randomization should be disregarded
Cardiac Biomarker Collection	Refer to Section 7.4.2 *Post-procedure Laboratory and Clinical Tests for complete details*

PROTOCOL 10-392

ABSORB IV
RANDOMIZED CONTROLLED TRIAL

A Clinical Evaluation of Absorb™ BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects with *de novo* Native Coronary Artery Lesions

Date	August 16, 2018
Principal Investigators and Study Chairman	**Principal Investigator & Study Chairman:** Gregg W. Stone, MD, Columbia University Medical Center, New York, NY **Co-Principal Investigators:** Stephen G. Ellis, MD, Cleveland Clinic, Cleveland OH Dean J. Kereiakes, MD, The Christ Hospital, Cincinnati, OH
Planned Number of Sites and Region(s)	Approximately 140 sites in the United States and outside the United States
Trial Type	Prospective, randomized, single-blind, multi-center trial
Sponsor / Data Monitoring/ Data Management/Data Analysis	Abbott Cardiovascular Systems, Inc. 3200 Lakeside Drive Santa Clara, CA 95054
Angiographic Core Laboratory	Cardiovascular Research Foundation, New York, NY
Ischemia Substudy Core Laboratory (SPECT and CT)	Cardiovascular Research Foundation, New York, NY
Clinical Events Committee	Cardiovascular Research Foundation, New York, NY
Data Safety Monitoring Board	Axio Research, Seattle, WA

TABLE OF CONTENTS

PROTOCOL SUMMARY FOR ABSORB IV

Investigational Device	Absorb™ Bioresorbable Vascular Scaffold (BVS) System[37]: • Scaffold diameters: 2.5, 3.0 and 3.5 mm • Scaffold lengths[38]: 8, 12, 18, and 28 mm Once Absorb GT1™ BVS System is commercially available, it can also be used in the ABSORB IV trial (see section 2.1.4 for available sizes).
Control Device	Commercially approved XIENCE Family Stent System, inclusive of XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro (OUS only), and XIENCE Pro^{X} (OUS only)[39]. • Stent diameters: 2.5, 2.75, 3.0, 3.25*, 3.5 and 4.0 mm • Stent lengths: 8, 12, 15, 18, 23, and 28 mm XIENCE Family Stent System will hereinafter be called "XIENCE" in this study. *The 3.25 mm is only available for XIENCE Xpedition.
Objectives	• **ABSORB IV Primary Objectives**: o To evaluate 30-day clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. o To evaluate long-term clinical outcomes of Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. • **ABSORB IV Secondary Objectives:**

[37] The commercially approved CE marked device will be used in geographies where it is commercially available.
[38] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 mm diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.
[39] For geographies where these devices are commercially available, the investigational sites may use only their locally approved devices.

	• To evaluate 1-year clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three de novo native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. o To evaluate the incidence of angina occurring within 1 year, with treatment of Absorb BVS compared to XIENCE.
Study Design	ABSORB IV is a prospective, randomized (1:1, Absorb BVS to XIENCE), single-blind, multi-center study, registering approximately 2600 subjects at approximately 140 sites. The enrollment of the ~2600 subjects in ABSORB IV will start after enrollment completion of the 2000 primary analysis subjects in ABSORB III.
Primary Endpoint	TLF through 30-day, tested for non-inferiority of Absorb BVS to XIENCE. • This analysis will consist of ~2600 subjects in ABSORB IV.
Powered Secondary Endpoints	1. TLF through 1 year, tested for non-inferiority of Absorb BVS to XIENCE. 2. Angina Powered Secondary Endpoint: The percentage of patients who experienced angina within 1 year, tested first for non-inferiority of Absorb BVS to XIENCE with reflex testing to superiority. • Angina is defined as any angina or angina equivalent symptoms determined by the physician and/or research coordinator after interview of the patient, and as adjudicated by a clinical events committee (CEC). • This analysis will exclude angina or angina equivalent symptoms that occurred following the index procedure through hospital discharge or 7 days, whichever occurs first. o For subjects who receive a planned staged procedure to treat one or more target lesions, the analysis will exclude angina or angina equivalent symptoms that occurred following the original index procedure through hospital discharge or 7 days after the final procedure, whichever occurs first.

	These analysis will consist of ~2600 subjects in ABSORB IV
Patient Reported Outcome (PRO) Informational Endpoints	Patient-reported outcomes (PRO) are informational endpoints to assess Health-Related Quality of Life. PRO assessments will be conducted at baseline, 1 and 6 months, and at 1, 3 and 5 years. The following questionnaires will be used in this study: • Seattle Angina Questionnaire-7 (SAQ-7) to assess disease-specific Quality of Life • EuroQoL 5D (EQ-5D) survey to assess overall health status (Note: PRO endpoints will be evaluated in the ~2600 subjects of ABSORB IV) The PROs will be analyzed to evaluate the relationship between quality of life and cardiovascular events that occurred post-PCI and to substantiate the clinical impact of the angina events identified in the trial.
Health Economics Informational Endpoints	The primary analysis is to compare the resource utilization and costs between the two treatment groups at 1, 2 and 3 years. If the rates of angina, hospitalizations or revascularizations are different between the two arms, a cost effectiveness analysis will be performed evaluating the cost of angina, hospitalizations or revascularizations avoided.
Subject Enrollment, Randomization and Registration	• Subjects are considered <u>enrolled</u> in ABSORB IV after signing the Informed Consent. • Subjects are considered <u>randomized</u> in ABSORB IV after the interactive voice response system (IVRS) has been called and a device (Absorb BVS or XIENCE) has been assigned. • Subjects are considered <u>registered</u> in the ABSORB IV upon randomization. • Enrolled subjects not randomized in the trial will be considered screen failures and will not be followed.
Clinical Follow-Up	All registered subjects in ABSORB IV will receive the following clinical follow-up: o 30 ± 7 days follow-up telephone contact/office visit o 90 ± 14 days follow-up telephone contact/office visit

	○ 180 ± 28 days follow-up telephone contact/office visit ○ 270 ± 28 days follow-up telephone contact/office visit ○ 1 year ± 28 days follow-up telephone contact/office visit ○ 2 years ± 28 days follow-up telephone contact/office visit ○ 3 years ± 28 days follow-up telephone contact/office visit ○ 4 years ± 28 days follow-up telephone contact/office visit ○ 5 years ± 28 days follow-up telephone contact/office visit
Patient Reported Outcome (PRO) Assessments	All registered subjects of ABSORB IV will receive the following PRO assessments: ○ Baseline: SAQ-7, EQ-5D ○ 30 ± 7 days: SAQ-7, EQ-5D ○ 180 ± 28 days: SAQ-7, EQ-5D ○ 1 year ± 28 days: SAQ-7, EQ-5D ○ SAQ-7, EQ-5D will also be administered to all registered subjects at 3 and 5 years (± 28 days) visits.
Primary Analysis Sample Size Justification	The sample size was originally based on a powered landmark analysis. The powered landmark analysis has since been removed, however, the sample size was sufficient to support the testing of the powered 30 day TLF primary endpoint and the powered secondary endpoints of 1 year TLF and 1 year angina.
Inclusion Criteria	**General Inclusion Criteria** 1. Subject must be at least 18 years of age. 2. Subject or a legally authorized representative must provide written Informed Consent prior to any study related procedure, per site requirements. 3. Subject must have evidence of myocardial ischemia (e.g., silent ischemia, stable or unstable angina, non-ST-segment elevation MI (NSTEMI)**, OR** recent ST-segment elevation MI (STEMI). Patients with stable coronary syndromes can be enrolled any time after symptom onset if eligibility criteria are otherwise

	met. Patients with acute coronary syndrome can be enrolled under the following conditions: a. Unstable angina or NSTEMI within 2 weeks of the index procedure. b. STEMI > 72 hours ≤ 2 weeks prior to the index procedure. Note: Subjects with UA or NSTEMI or STEMI occurring > 2 weeks of the index procedure can be included in the trial but should be categorized based on their current angina class. 4. Subjects must be suitable for PCI. Subjects with stable angina or silent ischemia and < 70% diameter stenosis must have objective signs of ischemia as determined by one of the following: abnormal stress echocardiogram, nuclear scan, ECG, PET, MRI, and/or fractional flow reserve (FFR). (**Note: subject with silent ischemia must have a prior history of typical angina, angina-equivalent symptoms, or atypical angina within the past year to be included in the trial.)** 5. Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery. 6. Female subject of childbearing potential who does not plan pregnancy for up to 1 year following the index procedure. For a female subject of childbearing potential a pregnancy test must be performed with negative results known within 7 days prior to the index procedure per site standard. 7. Female subject is not breast-feeding at the time of the screening visit and will not be breast-feeding for at least 1 year following the index procedure. 8. Subject agrees to not participate in any other investigational or invasive clinical study for a period of 5 years following the index procedure.[40] **Angiographic Inclusion Criteria** Treatment of up to three *de novo* lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial

[40] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

	vessel[41]. If only a single lesion is to be treated, it must be a target lesion. Up to one non-target lesion can be treated. Non-target lesion treatment can occur only in a non-target vessel. If there are two target lesions within the same epicardial vessel, the two target lesions must be at least 15 mm apart per visual estimation; otherwise this is considered as a single target lesion for lesion (and stent) length determination and must be treated with a single study device. 1. Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥50% and < 100%, with a TIMI flow of ≥ 1, and one of the following: stenosis ≥ 70%, an abnormal functional test (e.g., fractional flow reserve ≤0.80 AND/OR a positive stress test), or presentation with an acute coronary syndrome (unstable angina or NSTEMI within 2 weeks of index procedure, or STEMI >72 hours but ≤ 2 weeks prior to the index procedure). a. Target lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥ 2.50 mm and ≤ 3.75 mm.* b. Target lesion(s) must be located in a native coronary artery with length by visual estimation of ≤ 24 mm. Note: Subjects with UA or NSTEMI or STEMI occurring > 2 weeks of the index procedure can be included in the trial but should be categorized based on their current angina class. *Note: To exclude enrollment of excessively small vessels, if the operator believes that based on visual angiographic assessments, the distal reference vessel diameter is ≤ 2.75 mm such that the plan is to implant a 2.5 mm device (stent or scaffold) in a target lesion, it is strongly recommended that either on-line QCA or intravascular imaging (ultrasound or optical coherence tomography) is used and demonstrates that the measured distal RVD for this target lesion is ≥ 2.50 mm (by at least one of these imaging modalities). This measurement may be performed before or after pre-dilatation, but before randomization. If the distal RVD measures <2.5 mm, that lesion IS NOT ELIGIBLE for randomization. Such a lesion may be treated as a non-target lesion.

[41] The definition of epicardial vessels means the LAD, LCX and RCA and their branches.

Exclusion Criteria	**General Exclusion Criteria** 1. Any surgery requiring general anesthesia or discontinuation of aspirin and/or a P2Y12 receptor inhibitor is planned within 12 months after the procedure. 2. Subject has known hypersensitivity or contraindication to device material and its degradants (everolimus, poly (L-lactide), poly (DL-lactide), lactide, lactic acid) and cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoro polymers that cannot be adequately pre-medicated. Subject has a known contrast sensitivity that cannot be adequately pre-medicated. 3. Subject has known allergic reaction, hypersensitivity or contraindication to any of the following: aspirin; or clopidogrel and prasugrel and ticagrelor; or heparin and bivalirudin, and therefore cannot be adequately treated with study medications. 4. Subject had an acute STEMI (appropriate clinical syndrome with ≥1 mm of ST-segment elevation in ≥2 contiguous leads) within 72 hours of the index procedure. 5. Subject has a cardiac arrhythmia identified at the time of screening for which at least one of the following criteria is met:[42] a. Subject requires coumadin or any other agent for chronic oral anticoagulation. b. Subject is likely to become hemodynamically unstable due to their arrhythmia. c. Subject has poor survival prognosis due to their arrhythmia. 6. Subject has a left ventricular ejection fraction (LVEF) < 30% assessed by any quantitative method, including but not limited to echocardiography, MRI, multiple-gated acquisition (MUGA) scan, contrast left ventriculography, PET scan, etc. LVEF may be obtained within 6 months prior to the procedure for subjects with stable CAD. For subjects presenting with ACS, LVEF must be assessed within 1 week of the index procedure and after ACS presentation, which may include contrast left ventriculography during the index procedure but prior to randomization in order to confirm the subject's eligibility.

[42] Investigator should use discretion when enrolling subjects with high CHADS scores.

	7. Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if performed anytime >30 days before the index procedure, or between a minimum of 24 hours and 30 days before the index procedure if successful and uncomplicated. 8. Subject requires future staged PCI of any lesion other than a target lesion identified at the time of index procedure; or subject requires future peripheral vascular interventions < 30 days after the index procedure. 9. Subject has received any solid organ transplants or is on a waiting list for any solid organ transplants. 10. At the time of screening, the subject has a malignancy that is not in remission. 11. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy. 12. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum. 13. Subject is receiving or will require chronic anticoagulation therapy (e.g., coumadin, dabigatran, apixaban, rivaroxaban, edoxaban or any other related agent for any reason). 14. Subject has a platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3. 15. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B. 16. Subject has renal insufficiency as defined as an estimated GFR < 30 ml/min/1.73m^2 or dialysis at the time of screening.[43] 17. Subject is high risk of bleeding for any reason; has a history of bleeding diathesis or coagulopathy; has had a significant

[43] Estimated GFR can be based on Modification of Diet in Renal Disease (MDRD) equation or Cockcroft-Gault equation (CCG).

	gastrointestinal or significant urinary bleed within the past six months. 18. Subject has had a cerebrovascular accident or transient ischemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g. aneurysm, arteriovenous malformation, etc.). 19. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used. 20. Subject has a life expectancy <5 years for any non-cardiac or cardiac cause. 21. Subject is in the opinion of the Investigator or designee, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason. This includes completion of Patient Reported Outcome instruments. 22. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.[44] 23. Subject is part of a vulnerable population who, in the judgment of the investigator, is unable to give Informed Consent for reasons of incapacity, immaturity, adverse personal circumstances or lack of autonomy. This may include: Individuals with a mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention. **Angiographic Exclusion Criteria** All exclusion criteria apply to the target lesion(s) or target vessel(s).

[44] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

	1. Unsuccessful pre-dilatation, defined as the presence of one or more of the following (note: successful pre-dilatation of at least one target lesion is required prior to randomization): a. Residual %DS after pre-dilatation is ≥ 40% (per visual estimation). Note: achieving a %DS ≤ 20% prior to randomization is strongly recommended. b. TIMI flow grade <3 (per visual estimation). c. Any angiographic complication (e.g. distal embolization, side branch closure). d. Any dissection NHLBI grade D-F. e. Any chest pain lasting > 5 minutes. f. Any ST-segment depression or elevation lasting > 5 minutes. 2. Lesion is located in left main or there is a ≥30% diameter stenosis in the left main (unless the left main lesion is a protected left main (i.e. a patent bypass graft to the LAD and/or LCX arteries is present), and there is no intention to treat the protected left main lesion). 3. Aorto-ostial RCA lesion (within 3 mm of the ostium). 4. Lesion located within 3 mm of the origin of the LAD or LCX. 5. Lesion involving a bifurcation with a: a. side branch ≥ 2 mm in diameter, or b. side branch with either an ostial or non-ostial lesion with diameter stenosis >50%, or c. side branch requiring dilatation 6. Anatomy proximal to or within the lesion that may impair delivery of the Absorb BVS or XIENCE stent: a. Extreme angulation (≥ 90°) proximal to or within the target lesion. b. Excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion. c. Moderate or heavy calcification proximal to or within the target lesion. If IVUS used, subject must be excluded

<table>
<tr><td></td><td>if calcium arc in the vessel prior to the lesion or within the lesion is ≥ 180°.

7. Lesion or vessel involves a myocardial bridge.

8. Vessel has been previously treated with a stent and the target lesion is within 5 mm proximal or distal to a previously stented lesion.

9. Target lesion located within an arterial or saphenous vein graft or distal to any arterial or saphenous vein graft.</td></tr>
<tr><td>Lesion Selection</td><td>Prior to treatment with the assigned device (Absorb BVS or XIENCE), vessel sizing by visual estimation must be conducted to appropriately match the device to the size of the vessel. Quantitative methods such as on-line QCA, IVUS or OCT may be used if the site is experienced with these techniques. Specifically, use of pre-PCI and post-PCI IVUS or OCT is strongly recommended to optimize device sizing and results. Details on the vessel sizing methods can be found in the Imaging Guidance Document. Table 1.0 provides the device sizes, the reference vessel diameter (RVD) and lesion length for ABSORB IV.

Table 1.0 Absorb BVS and XIENCE Sizes in ABSORB IV
<table>
<tr><th rowspan="2">Device</th><th colspan="2">Lesion and Device Sizes</th></tr>
<tr><th>RVD [1]</th><th>Lesion Length[1]</th></tr>
<tr><td>Absorb BVS
(Target lesion)</td><td>RVD ≥ 2.50 mm - ≤ 3.75 mm

Scaffold diameter: 2.5, 3.0 and 3.5 mm</td><td>Lesion length ≤ 24 mm
Scaffold Length[2]: 8, 12, 18 and 28 mm [3]</td></tr>
<tr><td>XIENCE[4]
(Target lesion)</td><td>RVD ≥ 2.50 mm - ≤ 3.75 mm

Stent diameter: 2.5, 2.75, 3.0, 3.25 3.5, 4.0 mm</td><td>Lesion length ≤ 24 mm
Stent Length: 8, 12, 15, 18, 23 and 28 mm [3]</td></tr>
</table>
[1] Reference vessel diameter (RVD) and lesion length are based on visual estimation.
[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter. The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.
[3] For target lesion, planned overlapping is not allowed (i.e. the lesion must be eligible for treatment with a single stent). However, bailout overlapping is allowed if required.
[4] XIENCE V, XIENCE Prime, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^{X} will be used in this study.

It is highly recommended that a minimum of 2 mm (by visual estimation) of normal or nearly normal reference vessel at both proximal and distal edge be covered by the device.</td></tr>
</table>

Treatment Strategy	• Treatment of up to three *de novo* lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel[45]. • If only a single lesion is to be treated, it must be a target lesion, treated with the assigned device (Absorb or XIENCE). • Non-target lesion treatment can occur only in a non-target vessel. • The treatment possibilities are: o Single target lesions o Two or three target lesions o One target lesion and one non-target lesion o Two target lesions and one non-target lesion • All target lesions must meet angiographic inclusion/exclusion criteria. • The non-target lesion must be treated first with a XIENCE, before randomization, per the instructions for use (IFU). A non-target lesion cannot be considered for a staged procedure. The patient may then only be randomized if treatment of the non-target lesion was successful and uncomplicated, defined as: o final diameter stenosis ≤ 10% with final TIMI-3 flow, o with no residual dissection NHLBI grade ≥ type B, and o no transient or sustained angiographic complications (e.g., distal embolization, side branch closure), o no chest pain lasting > 5 minutes, and o no ST segment elevation or depression lasting > 5 minutes. • If there are two target lesions within the same epicardial vessel, the two target lesions must be at least 15 mm apart; otherwise this should be considered a single target lesion for lesion (and stent) length determination and must be treated with a single study device. **Access Site and Guide Catheter Size:** • Either femoral or radial access may be used.

[45] The definition of epicardial vessels means the LAD, LCX and RCA and their branches.

- A minimum 6F guide catheter or greater must be used during the index procedure per requirements for Absorb BVS implantation (refer to IFU).
    - Minimum guiding catheter compatibility (inner diameter) for Absorb BVS is 0.070”/1.8 mm (6F).
    - Devices (i.e., guide sheaths such as the GuideLiner) that decrease the inner diameter of the guide catheter outside of the Absorb BVS minimum guide catheter compatibility must not be used with the Absorb BVS System. Do not insert a 5-in-6, or a 6-in-7 guide sheath into a 6F or 7F guiding catheter, respectively, as doing so will result in an inner diameter that is too small for use with the Absorb BVS.
    - If a guide sheath is necessary, the inner diameter must meet or exceed the above minimum guiding catheter requirements for Absorb BVS (i.e., only the 7-in-8 GuideLiner provides an adequate inner diameter (0.071” ID), 8F guiding catheter would be required).
    - For XIENCE, please follow IFU for guiding catheter size.

Baseline angiogram and identification of the potential target lesion:

- Assessment of the potential target lesion(s) to be treated must be done to ensure angiographic criteria are met; this must occur prior to pre-dilatation and vessel sizing. Refer to the Imaging Guidance Document.
- To exclude enrollment of excessively small vessels, if the operator believes that based on visual angiographic assessments, the distal reference vessel diameter is ≤ 2.75 mm such that the plan is to implant a 2.5 mm device (stent or scaffold) in a target lesion, it is strongly recommended that either on-line QCA or intravascular imaging (ultrasound or optical coherence tomography) is used and demonstrates that the measured distal RVD for this target lesion is ≥ 2.50 mm (by at least one of these imaging modalities). This measurement may be performed before or after pre-dilatation, but before randomization. If the distal RVD measures <2.5 mm, that lesion IS NOT ELIGIBLE for randomization. Such a lesion may be treated as a non-target lesion.

Pre-dilatation of potential target lesion(s)

	• Pre-dilatation of at least one of the planned target lesions(s) must be performed and be successful before calling IVRS. However, each target lesion must be pre-dilated before device implantation in that lesion. • Pre-dilatation must be performed with an angioplasty balloon; cutting or scoring balloons may be used per physician discretion. • The pre-dilatation balloon should be sized 1:1 to the visually estimated RVD and should be no more than 0.25 mm smaller than RVD. If the pre-dilatation balloon is sized 1:1 a non-compliant balloon is strongly recommended. The pre-dilatation balloon must be equal in length or shorter than the planned scaffold/stent length. Important: Full balloon expansion with the pre-dilatation balloon must be achieved before the patient is randomized into the study. If there is any question that the target lesion was not fully dilated or that any significant resistance to expansion from the lesion remains, the lesion should be re-dilated with a non-compliant balloon (sized 1:1 to the RVD) at higher pressure. Absorb BVS or XIENCE must not be implanted in a lesion in which full balloon expansion has not been achieved. • The potential target lesion(s) must continue to meet angiographic criteria following adequate pre-dilatation, to be regarded as "successful pre-dilatation". o RVD remains ≥ 2.50 mm - ≤ 3.75 mm, and length of the lesion that will be covered by the device (including any edge dissections) is still ≤ 24 mm. o Residual %DS is a maximum of < 40% (per visual estimation); ≤ 20% is strongly recommended. o TIMI Grade 3 flow (per visual estimation). o No angiographic complications (e.g. distal embolization, side branch closure). o No dissections NHLBI grade D-F. o No chest pain lasting > 5 minutes. o No ST-segment depression or elevation lasting > 5 minutes.

- For two or three potential target lesions, the lesion with the highest possibility of failing eligibility criteria after pre-dilatation (per investigator's assessment) should be identified as the 1st target lesion and pre-dilated first before randomization.
    - If the 1st target lesion was successfully pre-dilated and eligibility criteria are still met, the operator may at this point choose to randomize the patient, or pre-dilate other lesions. If other lesions are pre-dilated, all such pre-dilatations must be considered successful according to the above criteria prior to randomization. If there are two target lesions in a single epicardial coronary artery, it is strongly recommended that both be successful pre-dilated before the patient is randomized. The IVRS is called to randomize the subject. All target lesions must be treated with the assigned device.
    - If the 1st target lesion was successfully pre-dilated but did not meet vessel sizing criteria, treat as a non-target lesion. Once the first lesion is successfully treated as a non-target lesion, the second lesion or third lesion must meet successful predilatation and vessel sizing criteria. Afterwards IVRS must be called and the target lesion(s) will be treated per assignment.
    - If pre-dilatation of the 1st target lesion fails (or if pre-dilatation of any lesion fails if multiple lesions are pre-dilated prior to randomization), the patient may not be randomized, and the interactive voice response system (IVRS) must not be called. The lesion will be treated with XIENCE or standard of care.
    - If the 1st target lesion was successfully pre-dilated but no longer met eligibility criteria (or if any lesion after pre-dilatation no longer met eligibility criteria if multiple lesions are pre-dilated prior to randomization), the patient may not be randomized, and the interactive voice response system (IVRS) must not be called.
    - If after successful pre-dilatation, randomization and treatment of the 1st target lesion with the assigned device, and pre-dilatation of the 2nd or 3rd target lesion failed, the patient is to be treated with XIENCE. For any lesion in which pre-dilatation did not meet the success definition, the default device is XIENCE.
- Each target vessel and lesion should also be such that the operator believes either the Absorb BVS or XIENCE devices could be delivered to and cross the target lesion after pre-

dilatation (e.g. absence of excessive vessel or lesion tortuosity or calcification).

Vessel Sizing

- Following the use of nitroglycerine (at least 100 µg intracoronary nitroglycerine, >150 µg preferred)[46] and successful pre-dilatation of the potential target lesion(s), vessel sizing must be conducted by visual estimation. If nitroglycerine is not available, intravenous nitroprusside or intravenous calcium channel blocker may be used per physician discretion.

- Quantitative methods such as on-line QCA, IVUS or OCT may be used if the site is experienced with these techniques, taking into account that QCA tends to under-estimate RVD compared to visual estimation and OCT, whereas IVUS tends to over-estimate lumen RVD compared to visual estimation and OCT. Specifically, use of pre-PCI and post-PCI IVUS or OCT is strongly recommended to optimize device sizing and results. Follow core laboratory guidelines for the use of each modality.

- Prior to randomization, IVUS or OCT can be used to evaluate the vessel if there is question regarding the eligibility of the vessel either before or after pre-dilatation. Specifically, to exclude enrollment of excessively small vessels, if the operator believes that based on visual angiographic assessments, the distal reference vessel diameter is ≤ 2.75 mm such that the plan is to implant a 2.5 mm device (stent or scaffold) in a target lesion, it is strongly recommended that either on-line QCA or intravascular imaging (ultrasound or optical coherence tomography) is used and demonstrates that the measured distal RVD for this target lesion is ≥ 2.50 mm (by at least one of these imaging modalities). This measurement may be performed before or after pre-dilatation, but before randomization. If the distal RVD measures <2.5 mm, that lesion IS NOT ELIGIBLE for randomization. Such a lesion may be treated as a non-target lesion. A subject must not be randomized in ABSORB IV if:

    - Vessel size or lesion length before or after pre-dilatation does not satisfy eligibility criteria.

    - Moderate or heavy calcification, tortuosity or other conditions are present proximal or within the target

[46] If the patient's blood pressure is so low that ≥ 100 ug of nitroglycerine cannot be administered, the patient should not be randomized. It is suggested that ≥200 µg of nitroglycerine be administered if the systolic blood pressure is >140 mmHg. Timing of nitroglycerine administration and pre-dilatation is per physician discretion, but must be before randomization and assessment of scaffold or stent size.

segment, reducing the likelihood that the Absorb BVS or XIENCE can be either delivered to or expanded at the lesion.

- Complications and/or adverse events were identified during IVUS or OCT usage (e.g. vessel dissection NHLBI grade D-F).[47]

- Table 2.0 provides the guidance of vessel and device sizing during the procedure, which are detailed as the following:
  - First, assess RVD based on visual estimation
  - Then, select a pre-dilatation balloon sized 1:1 to RVD or 0.25 mm smaller than RVD. For example, for RVD of 2.5 mm, a pre-dilatation balloon of 2.25 or 2.5 mm should be used.
  - Use the size of the inflated pre-dilatation balloon, as well as the results after pre-dilatation, to reassess the RVD for appropriate vessel sizing for the scaffold or stent. If the reassessed RVD after pre-dilatation exceeds the specified range for a specific BVS size, the next available size Absorb BVS can be used. For example, if the RVD is reassessed as 2.8 mm after pre-dilatation of a vessel that was believed to be 2.5 mm before pre-dilatation, then implant a 3.0 mm BVS.
  - Post-dilatation of the scaffold is strongly recommended for all Absorb treated lesions, especially for any implanted 2.5 mm ABSORB scaffolds.
  - For patients randomized to XIENCE, the decision to post-dilate should be made according to standard practice.
  - Post-dilatation must always be performed with a non-compliant balloon, sized 1:1 to the vessel, using at least 16 atm of pressure.. Always make sure the non-compliant post-dilatation balloon has a length short enough so it is inflated within the scaffold margins to avoid edge dissection. The delivery balloon should not be used for post-dilatation.

Table 2.0 Vessel and Device Sizing

[47] Examples of complications associated with IVUS or OCT: side-branch occlusion, persistent S-T abnormalities, prolonged chest pain, flow limiting dissections etc.

Closest RVD by Visual Estimation	Pre-dilatation Balloon Diameter	Reassessed Closest RVD after Pre-dilatation	Absorb BVS Diameter
2.5 mm	2.25 or 2.5 mm	2.5 mm	2.5 mm
2.75 mm	2.5 – 2.75 mm	2.75 mm	3.0 mm
3.0 mm	2.75 – 3.0 mm	3.0 mm	3.0 mm
3.25 mm	3.0 – 3.25 mm	3.25 mm	3.5 mm
3.5 mm	3.25 – 3.5 mm	3.5 mm	3.5 mm
3.75 mm	3.5 – 3.75 mm	3.75 mm	3.5 mm

Randomization

- Upon completion of successful pre-dilatation and vessel sizing of the first target lesion (or of multiple target lesions, at operator discretion as described above), the interactive voice response system (IVRS) can be called.
- A subject is considered registered and in the ITT population at the time of randomization.

Lesion Treatment

- It is highly recommended that the length of the Absorb BVS and XIENCE stent be selected to allow at least 2 mm of normal or nearly normal reference vessel at each edge.
- If the Absorb BVS cannot reach or cross the lesion or additional lesion preparation is required, the Absorb BVS must be removed and a new Absorb BVS must be introduced after subsequent pre-dilatation(s) with the same sized or larger non-compliant balloon at higher pressure. Note: the Absorb BVS should not be "Dottered" across the lesion if it does not cross easily.
- If the Absorb BVS is unable to reach or cross the target lesion after multiple attempts (maximum of two Absorb BVS; including additional lesion preparation), a XIENCE stent must be used.
- If XIENCE is unable to reach or cross the target lesion after multiple attempts (including additional lesion preparation), the investigator should treat the lesion per standard of care.
- In the case of two or three target lesions assigned to the Absorb BVS, if any of the target lesions is unsuccessfully treated with Absorb BVS, XIENCE must be used for that lesion. If the target lesion that failed treatment of Absorb BVS is treated

	successfully with XIENCE, the remaining target lesion(s) must be treated with Absorb BVS. • In the case of two or three target lesions assigned to XIENCE, if any of the target lesions is unsuccessfully treated with XIENCE, the investigator should treat the lesion per standard of care. If the target lesion that failed treatment with XIENCE is treated successfully with standard of care, the remaining target lesion(s) must be treated with XIENCE. • For patients in whom 2 or 3 target lesions will be treated, a maximum of one staged procedure is allowed. The decision to stage may be made prior to the first intervention, or immediately after the first intervention (depending on the complexity, contrast and radiation use of the first procedure). If a staged procedure becomes necessary, it is strongly recommended that the staged procedure occurs within 2 weeks of the index procedure, but in all cases no more than 35 days from the index procedure. The assigned device must be used for staged procedures. To avoid having to cross a previously implanted study device, it is strongly recommended that the staged lesion(s) be located in a separate epicardial vessel from the lesion(s) previously treated during the first intervention. • Successful lesion treatment is defined as final diameter stenosis ≤ 30% with final TIMI-3 flow, with no residual dissection NHLBI grade ≥ type B, and no transient or sustained angiographic complications (e.g. distal embolization, side branch closure), no chest pain lasting > 5 minutes, and no ST segment elevation or depression lasting > 5 minutes. • For Absorb BVS, the scaffold should be deployed slowly, by pressurizing the delivery system in 2 atm increments each over 5 seconds, until the scaffold is completely expanded. Pressure should be maintained for 30 seconds if tolerated by the patient. • For the Absorb BVS and XIENCE delivery balloon, do not exceed the rated burst pressure (RBP) per the IFU for the individual device. • Post-dilatation of target lesion treated with XIENCE should be per standard of care. • Post-dilatation of the scaffold is strongly recommended for all Absorb treated lesions, especially for any implanted 2.5 mm ABSORB scaffolds. If post-dilatation of the target lesion

treated with Absorb BVS is performed the following guidance is given:

- If a stent or scaffold cannot be re-crossed easily, excessive force with the balloon dilatation catheter or imaging catheter should be avoided. If it is necessary to re-cross the device, options to consider include changing the guide catheter orientation to reduce wire bias; consider use of a different wire or a wiggle wire or a buddy wire; attempt to cross the device with a balloon at 0 atm (rather than negative pressure); or inflate and deflate the balloon to wing it to help centralize the tip.

- A low profile, high pressure, non-compliant, balloon dilatation catheter that has not been previously inflated must be used.

- Post-dilatation must always be performed with a non-compliant balloon, sized 1:1 to the vessel, using at least 16 atm of pressure.

- The post-dilatation balloon length should be selected such that the balloon stays within the margins of the scaffold so as to avoid an edge dissection.

- The expanded diameter of the post dilatation balloon must be within the allowable expansion limits of the scaffold. Do not dilate the Absorb BVS beyond the dilatation limit which is 0.5 mm above the nominal diameter. Doing so may result in scaffold damage. Thus, it is highly recommended that the compliance chart of the non-compliant balloon selected be carefully reviewed prior to dilatation and an appropriate maximum pressure used to ensure that the scaffold is not over-dilated.

Table 3.0 Scaffold Diameter and Maximum Diameter Limit

Nominal Scaffold Diameter	Post Dilatation Maximum Diameter Limit
2.5 mm	**3.0 mm**
3.0 mm	**3.5 mm**
3.5 mm	**4.0 mm**

- The delivery balloon cannot be removed from the body and reinserted and used for post-dilatation.

	• During randomization, if a bailout device is required for a target lesion (e.g., for edge dissection), the same device as the implanted device must be used.
	  o Absorb BVS if target lesion is treated with Absorb BVS.
	  o XIENCE if target lesion is treated with XIENCE.
	  o If a bailout with an Absorb BVS device cannot be delivered to the site of the lesion, the device should be carefully withdrawn and a XIENCE used.
	  o If an appropriate size Absorb BVS is not available XIENCE can be used.
	• Overlap of the bailout stent/scaffold with the implanted stent/scaffold should be 1-2 mm; gaps should be avoided.
	• IVUS or OCT guidance may be used as per standard of care in all patients.
	• Please refer to the physician training deck for user guidance in handling procedural issues (e.g., difficulty in re-crossing an implanted scaffold for purposes such as intravascular imaging or post-dilatation if needed).
	• Unplanned Lesions
	  o In cases where treatment of a target lesion reveals unexpected additional lesion(s), the investigator may treat the lesion(s). This is considered an unplanned lesion.
	  o If the lesion meets enrollment criteria both before and after pre-dilatation, the lesion must be treated with the assigned device. This lesion will be considered to be an unplanned target lesion.
	  o If the lesion does not meet the enrollment criteria (either before or after pre-dilatation), the lesion must be treated with XIENCE. This lesion will be considered to be an unplanned non-target lesion.
	  o Planned treatment of more than two lesions per epicardial vessel or planned treatment of more than three lesions per subject is not allowed.

Antiplatelet[48] Therapy	**Antiplatelet Medication Loading Dose:** • Aspirin: Subjects must receive a loading dose of ≥ 300 mg of aspirin within 24 hours before the procedure, regardless of whether the patient was previously taking aspirin. For patients undergoing staged procedure who have not been discharged and have been prescribed daily aspirin while in hospital, no aspirin reloading is required. • P2Y12 receptor inhibitors: either clopidogrel, prasugrel or ticagrelor may be used as per standard of care and per label indications. o Clopidogrel: a peri-procedural loading dose 600 mg is required o Prasugrel: a peri-procedural loading dose of 60 mg is required o Ticagrelor: a peri-procedural loading dose of 180 mg is required. • For patients with stable coronary symptoms, silent ischemia, or acute coronary syndromes in whom all measured troponin and CK-MB values were within normal limits, pre-loading with clopidogrel between 3 and 24 hours prior to the procedure or prasugrel or ticagrelor between 1-24 hours prior to the index procedure is strongly recommended. If the above loading time periods are not possible, a P2Y12 inhibitor must be administered in all patients no later than 1 hour after the procedure. If the subject receives less than the required amount of the loading dose for a P2Y12 receptor inhibitor, the investigator is to give the remaining amount of the same agent in the next 24 hours and within the protocol required timeframe. **Note:** The biomarker measurements in patients with stable coronary symptoms and silent ischemia may be pending at the time of the procedure, or may be drawn from the arterial sheath prior to first balloon inflation; such patients may still be randomized, and a P2Y12 receptor inhibitor must be administered no later than 1 hour after the procedure. For patients with acute coronary syndromes in whom any troponin or CK-MB value at any time prior to the index hospitalization was elevated, one of two options must be given a) a loading dose of

[48] ABSORB IV will allow the use of FDA approved P2Y12 inhibitors. Loading and maintenance dosages of all P2Y12 inhibitors should follow respective prescribing information. If outside the US, country specific approvals are allowed.

	clopidogrel between 3 and 24 hours prior to the index procedure or prasugrel or ticagrelor between 1-24 hours prior to the index procedure OR b) an intravenous GP IIb/IIIa inhibitor or cangrelor (see below) prior to and/or during PCI but prior to first balloon inflation, per institution standard of care.. If an intravenous GP IIb/IIIa inhibitor is given, a P2Y12 receptor inhibitor must be given within 1 hour following the index procedure. If intravenous cangrelor is used, the timing of the first administration of the P2Y12 receptor inhibitor should be as follows: clopidogrel or prasugrel are administered at the time of discontinuation of the cangrelor infusion; ticagrelor may be administered before, during, or immediately upon discontinuation of the cangrelor infusion. Ticagrelor is the preferred P2Y12 receptor inhibitor in cangrelor-treated patients. Cangrelor should be maintained 2-4 hours post procedure according to product labeling. Note: If the subject receives less than the required amount of the loading dose for a P2Y12 receptor inhibitor, the investigator is to give the remaining amount of the same agent in the next 24 hours and within the protocol required timeframe. • The protocol required loading dose may be omitted in a) stable CAD or ACS patients maintained on chronic P2Y12 receptor inhibitor for ≥ 7 days, and b) patients who received a P2Y12 receptor inhibitor loading dose 1-7 days prior to the procedure and who have been maintained on a daily dose since. However, it is strongly recommended that stable patients on chronic clopidogrel are reloaded with a P2Y12 receptor inhibitor. For ACS patients on chronic clopidogrel, they must be reloaded with a P2Y12 receptor inhibitor if they did not already receive a loading dose of clopidogrel, prasugrel, or ticagrelor in the 24 hours prior to the procedure • Ticlopidine may be used as a substitute at a dose in accordance with standard hospital practice only if the subject develops hypersensitivity or intolerance to clopidogrel, prasugrel, or ticagrelor during the trial. • Refer to respective prescribing information for P2Y12 receptor inhibitor for further details regarding loading practice. • Cangrelor may be used pre-PCI at operator discretion as per local practice in any patient (but should be used similarly in patients randomized to ABSORB and XIENCE): a pre-PCI loading dose of 30 μg/kg IV followed by an IV infusion of 4 μg/kg for at least 2 hours and for a maximum of 4 hours may be used, in conjunction with an oral P2Y12 inhibitor. If ticagrelor is selected, the ticagrelor loading dose may be given before, during or immediately upon discontinuation of the cangrelor infusion. If clopidogrel or prasugrel

	are selected, a clopidogrel or prasugrel loading dose should be given immediately upon discontinuation of the cangrelor infusion, even if a loading dose was given earlier. **Antiplatelet Medication Post-Procedure Daily Dose:** • All subjects must be maintained at a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients*) or 90 mg twice daily of ticagrelor for a minimum of 12 months following the procedure. • All subjects must receive ≥75 to ≤100 mg of aspirin daily through 5 years follow-up during the study and should continue to take aspirin indefinitely. *For prasugrel subjects < 60 kg in weight or ≥ 75 years of age a maintenance dose of 5 mg per day for 12 months is recommended. Patients with prior stroke or TIA should receive clopidogrel or ticagrelor, and cannot be administered prasugrel. Refer to respective prescribing information for P2Y12 receptor inhibitor for further details regarding maintenance dose. **For subjects having staged procedures, the protocol-required pre-procedure and post-procedure antiplatelet regimens must be repeated for the staged procedure in the same manner as done for the original index procedure.**
Cardiac Biomarker Collection	**Between Baseline and Discharge** • All patients admitted with the diagnosis of possible acute coronary syndrome (including unstable angina, NSTEMI or STEMI) must have at least one and preferably 2 or more complete sets of cardiac biomarkers (a set consisting of troponin (I or T), CK and CK-MB) measured within 24 hours before the index procedure. Measurements should be at least 6 hours apart if multiple measurements are taken. Patients with stable coronary artery disease or silent ischemia must have a single set of cardiac biomarkers drawn. o If the patient has stable coronary artery disease or silent ischemia, the pre-procedure CK and CK-MB may be obtained during the procedure from the arterial sheath but prior to any angioplasty. The angioplasty may then proceed before the results are known. o To assist in determination of peri-procedural MI, all patients with an acute coronary syndrome (including unstable angina,

	NSTEMI or STEMI) must have troponin and CK and CK-MB drawn from the arterial sheath prior to first balloon inflation. o First post-procedure CK and CK-MB draw at 6 to 12 hours post-procedure. o Second post-procedure CK and CK-MB draw at 18-24 hours post-procedure, or at the time of discharge as long as discharge is at or after 16 hours post-procedure.* o If either of the post-procedure CK-MB levels are ≥ 5x ULN, serial CK and CK-MB levels must be drawn until they are falling. o A 12 lead ECG must be obtained at baseline and within 24 hours post procedure * For patients discharged prior to 16 hours, the subject will have to return to the enrolling institution for their second biomarker draw (or a visiting nurse may be sent to the patient's home to collect the blood sample). CK and CK-MB levels are required at each time point. Troponins are required pre-procedure and from the arterial sheath prior to first balloon inflation during the procedure in patients with acute coronary syndromes. All troponin, CK and CK-MB levels collected at any time points pre-procedure, during the procedure and post-procedure, should be documented in the electronic case report forms. For subjects having staged procedures, the protocol required pre-procedure and post-procedure cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure in the same manner as done for the original index procedure.
Primary Analytical Population	The primary analysis population will be the ITT population.

Note: Protocol 10-392 Part 1 (ABSORB III) compliance statement also applies to Part 2 (ABSORB IV).

1. INTRODUCTION

The ABSORB IV Randomized Controlled Trial (RCT) is designed to continue to evaluate the safety and effectiveness as well as the potential short and long-term benefits of Abbott Vascular Absorb™ Bioresorbable Vascular Scaffold (BVS) System[49] , and the Absorb GT1™ BVS System, as compared to the commercially approved, control stent XIENCE. In the subsequent sections of this protocol, the term "Absorb BVS" will be used to represent both Absorb™ BVS and Absorb GT1™ BVS.

ABSORB IV is a prospective, randomized (1:1 Absorb BVS to XIENCE), single-blind, multi-center trial, registering approximately 2600 subjects from approximately 140 sites[50] in the United States and outside the United States. The primary objective of ABSORB IV is to evaluate 30-day and long-term clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. The primary endpoint data of TLF through 30-day, tested for non-inferiority of Absorb BVS to XIENCE, will be tested on the ~2600 ABSORB IV subjects. The secondary objectives of ABSORB IV will be to evaluate TLF at 1-year and the incidence of angina occurring within 1 year, with treatment of Absorb BVS compared to XIENCE. The ABSORB IV protocol trial will compare patient reported outcomes, resource utilizations and costs between the Absorb BVS and XIENCE arms. These analyses will be based on all ~2600 subjects of ABSORB IV. The original design of the ABSORB IV trial also included an imaging ischemia sub-study aimed at providing the physiological and mechanistic evaluation of whether PCI treatment with Absorb BVS compared to XIENCE results in differences in myocardial ischemia in the early post-procedural period, and at 14 months and 62 months. However, this sub-study had to be stopped due to very slow enrollment (see **Section 12** for more details).

The enrollment/registration of ~2600 subjects in ABSORB IV will start after the completion of the enrollment/registration of 2000 primary analysis subjects in ABSORB III. All subjects in ABSORB IV will receive treatment of up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum two lesions in the same epicardial vessels with RVD $\geq$ 2.5 mm to $\leq$ 3.75 mm and lesion lengths $\leq$ 24 mm. All subjects will be screened per the protocol inclusion and exclusion criteria and all registered subjects will have clinical follow-up at 30, 90, 180, 270 days and 1, 2, 3, 4, and 5 years. In addition, all ~2600 subjects in ABSORB IV will complete patient-reported outcome self-administered questionnaires at baseline, 30, 180 days, and at 1 year. Additional PRO assessments may be conducted at 1, 3 and 5 years.

[49] The Absorb™ Bioresorbable Vascular Scaffold (BVS) System is the trade name for this product. During the course of development, multiple product names were used to describe this product including, Bioresorbable Vascular Scaffold (BVS) System, Bioabsorbable Vascular Stent, BVS Everolimus Eluting Coronary Stent System (EECSS), Abbott Vascular Bioabsorbable Device (AVBD) EECSS, BVS Cohort A (used in the ABSORB Cohort A trial) and BVS Cohort B (used in the ABSORB Cohort B trial).
[50] Majority sites in ABSORB IV also are participating sites in ABSORB III.

2. BACKGROUND INFORMATION

2.1.1 Name of the Investigational Device

The investigational device to be used in this trial is the Absorb BVS System[51] and the Absorb GT1™ BVS System once it is commercially available. In this protocol, the investigational scaffold or test device is referred to as "the Absorb BVS". The Absorb BVS System is manufactured by Abbott Cardiovascular Systems, Inc., California, an affiliate of Abbott Vascular, Inc.

2.1.2 Intended Indication

The Absorb Bioresorbable Vascular Scaffold (BVS) is a temporary scaffold that will fully resorb over time and is indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus and acute coronary syndromes, with ischemic heart disease due to de novo native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm.

2.1.3 Background Information

Please refer to **section 2.1.3 to 2.1.8** of ABSORB III Protocol (Version 17.0, August 16, 2018) for the detailed background information of the investigational device Absorb BVS, the control device XIENCE V, as well as the summary of pre-clinical and clinical studies.

2.1.4 Absorb GT1

Once Absorb GT1™ BVS System is commercially available, it can also be used in the ABSORB IV trial. The Absorb GT1 BVS System is composed of the following components:

- A bioresorbable poly(L-lactide) (PLLA) scaffold backbone
- A coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly(D,L-lactide) (PDLLA)
- Four platinum marker beads, two each embedded at the proximal and distal ends of the scaffold for radiopacity
- An optimized delivery system (ODS) that leverages technology advancements of the XIENCE family of products, and incorporates design features from the Absorb BVS, XIENCE Xpedition®, and XIENCE Alpine delivery systems

The Absorb GT1 sizes are detailed in the table below.

[51] The commercially approved CE marked device will be used in geographies where it is commercially available.

Table 2.1: Absorb GT1 BVS System Size Matrix

Scaffold Design	Product Diameter (mm)	Product Length (mm)				
		8	12	18	23*	28
Small	2.5	X	X	X	X	X
	3.0	X	X	X	X	X
Medium	3.5	N/A	X	X	X	X

* The commercially approved 23mm Absorb BVS GT1 device will not be used in ABSORB IV.

2.2 Trial Rationale

The Absorb BVS has been evaluated and continues to be evaluated in the ABSORB Family of Trials which includes ABSORB Cohort A and Cohort B, ABSORB EXTEND, ABSORB II and the ABSORB III Pivotal US trial. Retrospective comparison of Absorb BVS to XIENCE has demonstrated comparable TLF rates through 2 and 3 years (EXTEND 2-year TLF[52]: 6.2% vs. 8.2%; Cohort B 3-year TLF[53]: 9.9% vs. 11.4%). The potential long-term clinical benefit of Absorb BVS compared to metallic drug eluting stents has not been prospectively evaluated in randomized subject population.

Recurring angina has been associated with lifestyle limitations and worse self-reported quality of life, making the relief of symptoms one of the primary reasons for performing PCI[54]. However, despite symptom relief with stenting, post-PCI angina recurrence is a clinically relevant burden that impacts patient's quality of life. Recent retrospective descriptive comparison of Absorb BVS to XIENCE has shown preliminary evidence that Absorb BVS may be associated with lower rate of angina compared to XIENCE at 1 year (16% vs. 27.9%)[55]. As Absorb BVS is a novel technology it will be important to evaluate the potential to reduce the recurrence of angina post PCI compared to existing DES technologies. The ABSORB IV trial will further evaluate the differences between Absorb BVS and XIENCE in the percentage of patients with angina after the stenting procedure, as determined by physician and/or research coordinator after interview of the patient, and as adjudicated by a clinical events committee (CEC).

3. TRIAL OBJECTIVE

ABSORB IV Primary Objective:

[52] Whitbourn RJ. ABSORB EXTEND: An interim report on the 24-month clinical outcomes from the first 240 patients enrolled. TCT 2013.
[53] Serruys PW, Onuma Y, Garcia-Garcia H. First report of the three year clinical and multi-modality imaging results of the ABSORB trial evaluating the Absorb everolimus eluting bioresorbable vascular scaffold in the treatment of patients with De Novo native coronary artery lesions. ACC 2013.
[54] Holubkov R, Laskey WK, Haviland A, et al. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. *Am Heart J.* Nov 2002;144(5):826-833
[55] Stone GW. Demonstration of Clinical Superiority with a Bioresorbable Vascular Scaffold: The ABSORB IV Clinical Trial. http://www.tctmd.com/show.aspx?id=120552

- To evaluate 30-day clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial

- To evaluate long-term clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel.

ABSORB IV Secondary Objectives:

- To evaluate 1-year clinical outcomes of the Absorb BVS compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial

- To evaluate the incidence of angina occurring within 1 year with treatment of Absorb BVS compared to XIENCE.

4. CLINICAL TRIAL/INVESTIGATION FLOW AND FOLLOW-UP SCHEDULE

4.1 Number of Subjects to be Registered

Approximately 2600 subjects will be registered in ABSORB IV from approximately 140 sites in the United States and outside the United States. The enrollment/registration of ABSORB IV will start after the completion of enrollment/registration of the 2000 primary analysis subjects of ABSORB III.

4.2 ABSORB Physician Training

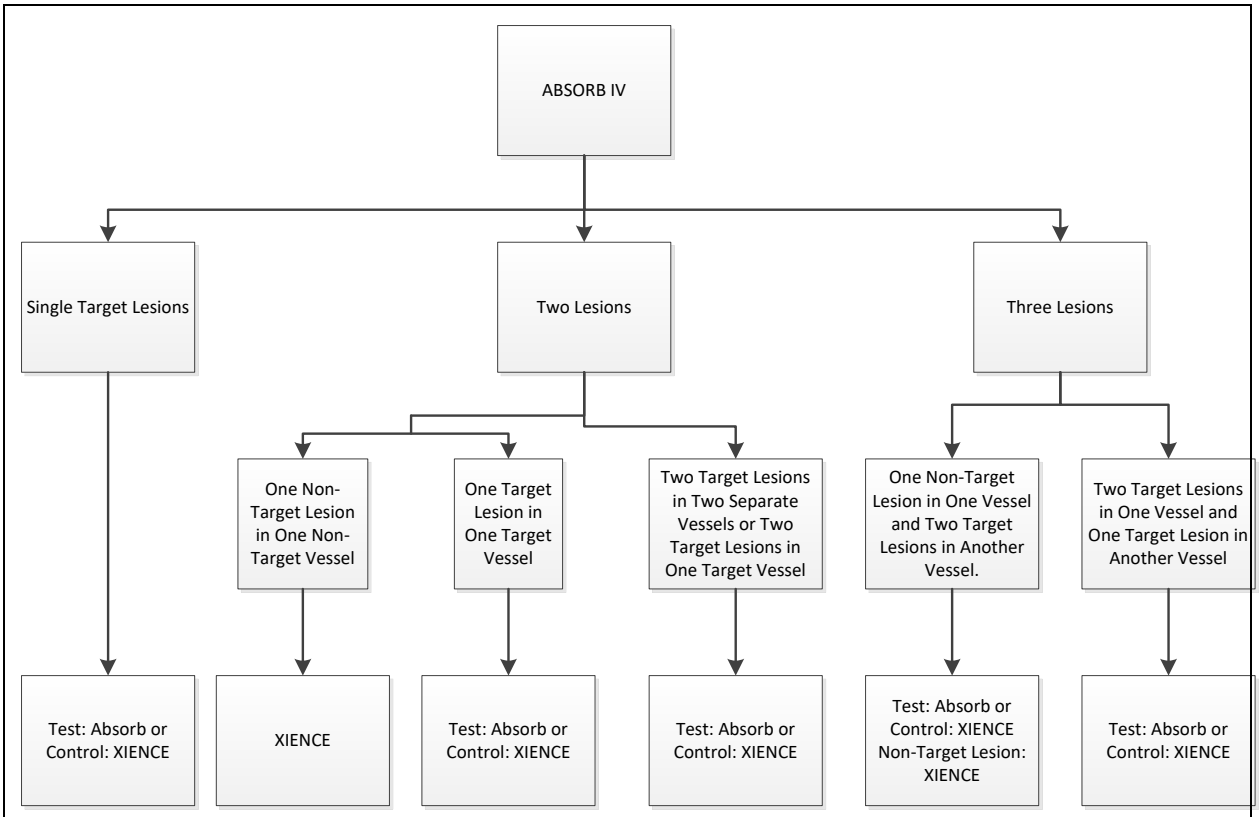
Investigators that have not participated in previous ABSORB trials or are not commercial users of the Absorb BVS device will participate in the ABSORB IV physician training program. Please refer to **section 4.2** of ABSORB III Protocol (Version 17.0, August 09, 2018) for the detailed information on the didactic training.

4.3 ABSORB IV Treatment Flow and Lesion Selection

A maximum of three *de novo* native coronary artery lesions will be treated in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. If there are two target lesions within the same epicardial vessel, the two target lesions must be at least 15 mm apart. One planned non-target lesion is allowed in ABSORB IV treated with a XIENCE per the IFU. However, in situations where treatment of a target lesion reveals additional lesion(s), the investigator may treat the lesion(s). This is considered an unplanned lesion. If the lesion meets enrollment criteria both before and after pre-dilatation, the lesion must be treated with the assigned device and will be considered to be an unplanned target lesion. If the lesion does not

meet the enrollment criteria (either before or after pre-dilatation), the lesion must be treated with XIENCE. This lesion will be considered as an unplanned non-target lesion.

Figure 4.1 shows the lesion treatment for subjects in ABSORB IV.



Note: For subjects with two or three target lesions in a maximum of two epicardial vessels, a maximum of two target lesions can be located within one epicardial vessel.

Figure 4.1 Lesion Treatment

Every attempt should be made that the two or three target lesion treatments occur at the same index procedure. However, if a staged procedure becomes necessary (e.g. due to high use of contrast or radiation after treatment of the first lesion), it is strongly recommended that the staged procedure occurs within 2 weeks of the index procedure using the assigned device, but in all cases no more than 35 days from the index procedure. To avoid having to cross a previously implanted study device, it is strongly recommended that the staged lesion(s) be located in a separate epicardial vessel from the lesion(s) previously treated during the first intervention. A maximum of one staged procedure is allowed. Staged procedures must only include target lesions identified at the time of the index procedure.

Prior to treatment with the assigned device (Absorb BVS or XIENCE), vessel sizing by visual estimation must be conducted to appropriately match the device to the size of the vessel. Quantitative methods such as on-line QCA, IVUS or OCT may be used if the site is experienced with these techniques. Specifically, use of pre-PCI and post-PCI IVUS or OCT is strongly

recommended to optimize device sizing results. Details on the vessel sizing methods can be found in **Imaging Guidance Document**.

To exclude enrollment of excessively small vessels, if the operator believes that based on visual angiographic assessments, the distal reference vessel diameter is ≤ 2.75 mm such that the plan is to implant a 2.5 mm device (stent or scaffold) in a target lesion, it is strongly recommended that either on-line QCA or intravascular imaging (ultrasound or optical coherence tomography) is used and demonstrates that the measured distal RVD for this target lesion is ≥ 2.50 mm (by at least one of these imaging modalities). This measurement may be performed before or after pre-dilatation, but before randomization. If the distal RVD measures <2.5 mm, that lesion IS NOT ELIGIBLE for randomization. Such a lesion may be treated as a non-target lesion. **Table 4.1** provides the device sizes, RVD and lesion length for ABSORB IV.

Table 4.1 Absorb BVS and XIENCE Sizes

	Lesion and Device Sizes	
Device	RVD [1]	Lesion Length[1]
Absorb BVS (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Scaffold diameter: 2.5, 3.0 and 3.5 mm	Lesion length ≤ 24 mm Scaffold Length[2]: 8, 12, 18 and 28 mm [3]
XIENCE[4] (Target lesion)	RVD ≥ 2.50 mm - ≤ 3.75 mm Stent diameter: 2.5, 2.75, 3.0, 3.25 3.5, 4.0 mm	Lesion length ≤ 24 mm Stent Length: 8, 12, 15, 18, 23 and 28 mm [3]

[1] Reference vessel diameter (RVD) and lesion length based on visual estimation
[2] Both the 8 mm and 12 mm lengths will be available for the 2.5/3.0 diameter Absorb BVS. Only the 12 mm length will be available for the 3.5 mm diameter.
[3] For target lesion, planned overlapping is not allowed (i.e., the lesion must be eligible for treatment with a single stent). However, bailout overlapping is allowed if required.
[4] XIENCE V, XIENCE Prime, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro, and XIENCE Pro^X will be used in this study.

The commercially approved CE marked 23mm Absorb BVS device will not be used in this study.

It is highly recommended a minimum of 2 mm (by visual estimation) of minimally diseased tissue be covered by the device at both the proximal and distal edges.

Planned overlap of the target lesion is not allowed. Overlap in the case of bailout is allowed. Please refer to **Section 7.3.5** for details regarding bailout.

4.4 Measures Taken to Avoid and Minimize Bias

In ABSORB IV there will be several measures taken to avoid and minimize bias such as randomization and blinding. This process is detailed in the following sections.

4.4.1 Randomization

Stratified Randomization:

Approximately 2600 subjects will be randomized 1:1 in the ABSORB IV trial (test device: Absorb BVS vs. control device: XIENCE). Randomization will be stratified by diabetes mellitus (diabetic vs. non-diabetic) and ABSORB III-like or not. ABSORB III-like will be determined by

the absence of planned staged procedure, number of target lesions ≤ 2, and no biomarker positive ACS or STEMI. Subjects will also be stratified by site at pre-specified expected high-enrolling sites. Other sites will be combined to ensure a sufficient number of subjects for the attainment of the desired randomization ratio. A centralized randomization service, IVRS, will be used.

Timing of Randomization:

Randomization will be done after successful and uncomplicated pre-dilatation of at least one target lesion and vessel sizing (refer to **Protocol Summary**, Treatment Strategy, for details). If there is a non-target lesion, it must be successfully treated prior to randomization. If there are two or three target lesions, after the first target lesion was successfully pre-dilated and vessel sizing criteria still met, the operator may at this point choose to randomize the patient, or pre-dilate other lesions. If other lesions are pre-dilated, all such pre-dilatations must be considered successful according to the above criteria prior to randomization. If there are two target lesions in a single epicardial coronary artery, it is strongly recommended that both be successfully pre-dilated before the patient is randomized.

Once randomization is completed and a treatment is assigned, the assigned device must be used for all lesions. An Absorb BVS scaffold may never be used in a patient randomized to XIENCE. However, if the patient is randomized to Absorb BVS and the scaffold cannot be delivered or a complication otherwise develops that requires treatment with a drug-eluting stent, a XIENCE stent must be used. If the XIENCE stent is unable to successfully treat the patient, any commercially available device approved for use in that geography may be used as necessary in the best interests of the patient. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment.

The subject is considered to be successfully registered in this study and considered in the ITT population at the point of randomization (refer to Section 6.4). Refer to **Appendix IV (Figure 1 and 2**) for enrollment and registration timeline and flow chart.

4.4.2 Blinding

This is a single-blinded clinical trial. Subjects will be blinded to their treatment assignment and the study site personnel will be trained not to disclose the treatment assignment to the subject. In addition to standard procedural sedation, headphones will be worn by the patient during the procedure to reduce the possibility of unblinding. Additionally, blinded site personnel, not present at the index procedure, will be assigned to conduct the clinical follow-up and they will be provided with a standard follow-up interview in order to reduce bias and maintain subject blinding. Subject blinding should be maintained until the 5-year follow-up visit for all registered subjects is completed.

The physician performing the procedure will not be blinded to the assigned treatment. Thus, if clinical follow-up with a study physician is deemed necessary at the protocol required follow-up time points, a different physician (or designee) than the one who implanted the device(s) must conduct the follow-up clinical visits in order to maintain subject blinding. Similarly, follow-up visits with research personnel must be conducted by different persons than those who were unblinded during the index hospitalization. Site personnel will be adequately trained such that the physician (or designee) conducting the clinical follow-up is adequately blinded to the treatment received by the subject. For unscheduled visits, subjects may see the physician who

implanted the device(s). Treating physician should prevent unblinding of the subject when they conduct any non-protocol related visits. In addition, hospital notes, dictated notes, notes to referral physicians, billing information, and other related patient information must refer to the assigned treatment device as "study device" or other non-revealing language, to maintain the blind. The only exception to these requirements is if the hospital billing department does not allow this practice. Sites will be provided with a blinding guidance document that will instruct the sites on how to maintain blinding at the clinical sites.

The Clinical Events Committee (CEC) will be blinded to the randomization assignments. The angiographic core laboratories cannot be blinded to the device received. The Data Safety Monitoring Board (DSMB) will also be blinded to the subject's randomization. Independent statisticians will generate blinded tables for review by the DSMB. The DSMB may request unblinded data if a safety signal is observed.

Sponsor personnel that will be unblinded will be the independent biostatisticians involved in generating and verifying the randomization code, key Clinical Science and Operations, Clinical Safety Monitors, Site Monitors, Clinical Data Management, Electronic Database Programmer, Inventory Management staff, and Clinical Information System (IS) personnel working on the trial. Restricted access of blinded personnel to the clinical database will be maintained until unblinding of the study.

4.5 Early Termination of the Clinical Trial

Please refer to **section 4.6** of ABSORB III Protocol (Version 17.0, August 09, 2018) for the relevant information about trial early termination.

5. ENDPOINTS

5.1 Primary Endpoints

TLF through 30-day, tested for non-inferiority against the control

- This analysis will consist of ~2600 subjects in ABSORB IV.
- TLF is defined as composite of Cardiac Death, Myocardial Infarction (per protocol-defined MI definition, Appendix II) attributable to Target Vessel (TV-MI), or Ischemia-Driven Target Lesion Revascularization (ID-TLR).

5.2 ABSORB IV Major Secondary Endpoint

- **TLF through 1-year, tested for non-inferiority against the control**
- **ABSORB IV Angina Powered Secondary Endpoint**: The percentage of patients who experienced angina within 1 year, tested first for non-inferiority with reflex to superiority against the control.
    - Angina is defined as any angina or angina equivalent symptoms determined by the physician and/or research coordinator after interview of the patient, and as adjudicated by a clinical events committee (CEC).

- This analysis will exclude angina or angina equivalent symptoms that occurred following the index procedure through hospital discharge or 7 days, whichever occurs first.

- This analysis will consist of ~2600 subjects in ABSORB IV.

5.3 Additional Secondary Endpoint(s)

In ABSORB IV the following clinical secondary endpoints will be analyzed for all the ~2600 subjects.

- **Acute Success**: (Combined Clinical/Angiographic Endpoint)
  - Device success (Lesion level analysis)
  - Procedural success (Subject level analysis)
- **Clinical Endpoint** in hospital and at each follow-up point (30, 90, 180, 270 days; 1, 2, 3, 4, 5 years).
  - **Component**
    - Death (Cardiac, Vascular, Non-cardiovascular)
    - Myocardial Infarction
      - Attributable to target vessel (TV-MI)
      - Not attributable to target vessel (NTV-MI)
    - Target Lesion Revascularization (TLR)
      - Ischemia driven TLR (ID-TLR)
      - Non ID TLR (NID-TLR)
    - Target Vessel Revascularization (TVR,)
      - ID TVR
      - Non ID TVR
    - All coronary revascularization
  - **Composite Endpoints**
    - Death/All MI
    - Cardiac Death/All MI

- Cardiac Death/TV-MI/ID-TLR (TLF)
- Cardiac Death/All MI/ID-TLR (MACE)
- Cardiac Death/All MI/ID-TLR/ID-TVR, non TL (Target Vessel Failure, TVF)
- Death/All MI/All revascularization

- **Scaffold-Thrombosis / Stent Thrombosis (per ARC definition)**
  - Timing (acute, sub-acute, late and very late)
  - Evidence (Definite and Probable)
- Rehospitalization
  - Coronary artery disease related
  - Cardiovascular, non-CAD related
  - Non-cardiovascular related
- Repeat coronary arteriography
- TLF through 5 years based on 4600 subjects (2000 primary analysis subjects of ABSORB III and 2600 subjects of ABSORB IV)

5.4 Informational Endpoints

5.4.1 Patient Reported Outcomes

Patient-reported outcomes are informational endpoints to assess Health-Related Quality of Life at baseline, 1, 6, 12 months and will be assessed at 3 and 5 years throughout the remaining duration of the trial. These PRO endpoints will be evaluated in the ~2600 subjects of ABSORB IV. The following questionnaires will be used in this study:

- Seattle Angina Questionnaire-7 (SAQ-7) to assess disease-specific Quality of Life
- EuroQoL 5D (EQ-5D) survey to assess overall health status

The PROs will be analyzed to evaluate the relationship between quality of life and cardiovascular events that occurs post-PCI and to substantiate the clinical impact of the angina events identified in the trial.

5.4.2 Health Economics

During the course of the trial, the Sponsor (or the health economic core laboratory) will collect health economic data. The data may include billing information and claims data for the index hospitalization and for subsequent hospitalizations during the follow-up period, for sites located in the United States only. Patients will be asked to provide consent to access billing information for the purposes of conducting economic analysis of the trial.

Additional information regarding medical resource utilization may also be collected throughout the trial, including but not limited to: laboratory services, diagnostic procedures, or pharmacy records.

6. SUBJECT SELECTION AND WITHDRAWAL

6.1 Subject Population

Subjects registered into this Clinical Investigation will be male and female subjects derived from the general interventional cardiology population. The Clinical Investigation will register approximately 2600 subjects, with up to three *de novo* native coronary artery lesions in a maximum of two epicardial vessels and a maximum of two lesions per epicardial vessel, who meet all eligibility criteria, have provided written Informed Consent and have been registered in the trial.

6.2 Subject Screening and Informed Consent

6.2.1 Subject Screening and Informed Consent

Please refer to **section 6.2.1** and **6.2.2** of ABSORB III Protocol (Version 17.0, August 16, 2018) for the relevant information about subject screening and informed consent.

6.3 Eligibility Criteria

Assessment for general eligibility criteria is based on the medical records of the site and interview with a candidate subject. Clinical and laboratory test of the eligibility assessment shall be per site standard of care. If some of the protocol required tests are not included in the site's standard tests, they must be done, but after written Informed Consent has been obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical evaluation. If ANY of the exclusion criteria are met, the subject is excluded from the clinical evaluation and cannot be registered. Please see **Protocol Summary,** Inclusion Criteria and Exclusion Criteria, for details of the eligibility criteria of ABSORB IV.

6.4 Point of Registration

During the randomization phase, the subject is considered randomized after IVRS has been called and a device has been assigned (Absorb BVS or XIENCE). The subject is considered registered and in the ITT population at the point of randomization. Once randomization is completed and a treatment arm is assigned, crossover is not permitted. Regardless of the actual device the subject received, the subject will be included in ITT population per the original randomization assignment.

Refer to **Appendix IV** and **Figures 1 and 2** for further registration details.

6.5 Subject Discontinuation

Please refer to **section 6.5** of ABSORB III Protocol (Version 17.0, August 16, 2018) for the relevant information about subject discontinuation.

7. TREATMENT AND EVALUATION OF SAFETY AND EFFECTIVENESS

7.1 Baseline

7.1.1 Baseline Laboratory Assessments to Confirm Subject Eligibility

Subject preparation will be in accordance with standard hospital policy for the care of interventional cardiology subjects.

7.1.2 Subject History

Subject history will include demographics (e.g., age, gender)[56], cardiac history including but not limited to Canadian Cardiovascular Society (CCS) and Braunwald classification of angina, history of myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, previous CABG and PCI, and concomitant cardiovascular medications (Refer to **Appendix II** for Definitions). In addition, measurements of weight, height, and resting blood pressure will be collected.

7.1.3 Patient-Reported Outcomes Assessment

All ~2600 subjects in ABSORB IV will complete the following Patient Reported Outcome questionnaires prior to the index procedure*.

- EuroQoL 5D (EQ-5D) survey to assess overall health status.
- Seattle Angina Questionnaire-7 (SAQ-7) to assess disease-specific Quality of Life.

Please refer to **section 7.1.3** of ABSORB III protocol (Version 17.0, August 16, 2018) for the details regarding each questionnaire.

*Every effort should be made to have subjects complete all three patient reported outcomes questionnaires prior to the procedure. However, in situations where this is absolutely not possible, subjects may complete them post-procedure, prior to discharge. Subjects who complete their questionnaires post-procedure should base their responses on their condition prior to the procedure.

7.2 Pre-Procedure

7.2.1 Pre-Procedure Laboratory Assessment

The following laboratory assessments need to be obtained prior to the index procedure or at the time of the index procedure depending on the assessment and condition of the subject.

Table 7.1 Baseline Laboratory Assessment

[56] Demographics include age, gender, post-menopausal status, date of birth, race/ethnicity, highest level of education, employment status and household income.

Within 21 days prior to procedure†	**Within 7 days prior to procedure**	**Within 48 hours prior to procedure**
Platelet and White Blood Count	Pregnancy test (if applicable)	12-lead ECG (within 24 hours preferred)
Hemoglobin		Creatine kinase (CK)
Serum Creatinine		Creatine kinase myocardial-band isoenzyme (CK-MB)
HbA1c‡		Troponin (if suspected acute coronary syndrome, within 24 hours)
Estimated GFR*		

†The 21-day lab results must be known prior to index procedure.
‡ HbA1c is to be collected in diabetic subjects only, and its result is not needed prior to the index procedure.
* Glomerular Filtration Rate

The following applies to cardiac enzyme measurement pre-procedure and during the procedure.

- All patients admitted with the diagnosis of possible acute coronary syndrome (including unstable angina, NSTEMI or STEMI) must have at least one and preferably 2 or more complete sets of cardiac biomarkers (a set consisting of troponin (I or T), CK and CK-MB) measured within 24 hours of procedure. Measurements should be at least 6 hours apart if multiple measurements were taken.

- If the patient has stable coronary artery disease or silent ischemia, a pre-procedure CK and CK-MB must be drawn, but may be obtained during the procedure from the arterial sheath but prior to any angioplasty. The angioplasty procedure may then be performed before the results are known.

- To assist in the determination of peri-procedural MI, during the procedure, all patients with an acute coronary syndrome (including unstable angina, NSTEMI or STEMI) must have troponin, CK and CK-MB drawn from the arterial sheath prior to first balloon inflation.

For subjects having staged procedures, the protocol-required pre-procedure and post-procedure cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure in the same manner as done for the original index procedure.

7.2.2 Dual Anti-Platelet Medications

Subjects selected for treatment with Absorb BVS or XIENCE must receive a loading dose of ≥ 300 mg of aspirin within 24 hours, regardless of whether the patient was previously taking aspirin. For patients undergoing staged procedure who have not been discharged and have been prescribed daily aspirin while in hospital, no aspirin reloading is required.

For patients with stable coronary symptoms, silent ischemia, or acute coronary syndromes in whom all measured troponin and CK-MB values were within normal limits, pre-loading with clopidogrel between 3 and 24 hours prior to the index procedure or prasugrel or ticagrelor between 1-24 hours prior to the index procedure is strongly recommended. If the above loading time periods are not possible, the P2Y12 inhibitor must be administered in all patients no later than 1 hour after the procedure. If the subject receives less than the required amount of the loading dose for a P2Y12 receptor inhibitor, the investigator is to give the remaining amount of the same agent in the next 24 hours and within the protocol required timeframe.

Note: The biomarker measurements in patients with stable coronary symptoms and silent ischemia may be pending at the time of the procedure, or may be drawn from the arterial sheath prior to first balloon inflation; such patients may still be randomized, and a P2Y12 receptor inhibitor must be administered no later than 1 hour after the procedure.

For patients with acute coronary syndromes in whom any troponin or CK-MB value at any time prior to the index hospitalization was elevated, one of two treatment options must be used a) a loading dose of clopidogrel between 3 and 24 hours prior to the procedure or prasugrel or ticagrelor between 1-24 hours prior to the index procedure must be given, OR b) an intravenous GP IIb/IIIa inhibitor or cangrelor (see below) must be administered prior to and/or during PCI but prior to first balloon inflation, per institution standard of care. If an intravenous GP IIb/IIIa inhibitor is given, a P2Y12 receptor inhibitor must be given within 1 hour following the index procedure. If intravenous cangrelor is used, the timing of the first administration of the P2Y12 receptor inhibitor should be as follows: clopidogrel or prasugrel are administered at the time of discontinuation of the cangrelor infusion; ticagrelor may be administered before, during, or immediately upon discontinuation of the cangrelor infusion. Ticagrelor is the preferred P2Y12 receptor inhibitor in cangrelor-treated patients. Cangrelor should be maintained 2-4 hours post procedure according to label.

Note: If the subject receives less than the required amount of the loading dose for a P2Y12 receptor inhibitor, the investigator is to give the remaining amount of the same agent in the next 24 hours and within the protocol required timeframe.

The protocol required loading dose may be omitted in a) stable CAD or ACS patients maintained on chronic P2Y12 receptor inhibitor for ≥ 7 days, and b) patients who received aP2Y12 receptor inhibitor loading dose 1-7 days prior to the procedure and who have been maintained on a daily dose since. However, it is strongly recommended that stable patients on chronic clopidogrel are reloaded with a P2Y12 receptor inhibitor. For ACS patients on chronic clopidogrel, they must be reloaded with a P2Y12 receptor inhibitor if they did not already receive a loading dose of clopidogrel, prasugrel, or ticagrelor in the 24 hours prior to the procedure.

Ticlopidine may be used as a substitute at a dose in accordance with standard hospital practice only if the subject develops hypersensitivity or intolerance to clopidogrel, prasugrel, or ticagrelor during the trial.

Refer to respective prescribing information for P2Y12 receptor inhibitor for further details regarding loading practice.

Cangrelor may be used pre-PCI at operator discretion as per local practice in any patient (but should be used similarly in patients randomized to ABSORB and XIENCE): a pre-PCI loading dose of 30 μg/kg IV followed by an IV infusion of 4 μg/kg for at least 2 hours and for a maximum of 4 hours may be used, in conjunction with an oral P2Y12 inhibitor. If ticagrelor is selected, the ticagrelor loading dose may be given before, during or immediately upon discontinuation of the cangrelor infusion. If clopidogrel or prasugrel are selected, a clopidogrel or prasugrel loading dose should be given immediately upon discontinuation of the cangrelor infusion, even if a loading dose was given earlier.

For subjects having staged procedures, the pre-procedure administration regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be repeated prior to the staged

procedure in the same manner as done for the original index procedure. If the subject has not been discharged between the index and staged procedures, and has received daily aspirin while in hospital, no aspirin reloading is required (see above).

7.2.3 Anticoagulation Medications

Subjects must receive appropriate anticoagulation and other therapy according to standard hospital practice. Either unfractionated heparin or bivalirudin may be used for procedural anticoagulation, as per the discretion of the investigator. Subjects having been treated with low molecular weight heparin (LMWH) prior to the procedure should receive their last dose more than 8 hours prior to the index procedure, and then be anticoagulated during the procedure with either unfractionated heparin or bivalirudin. LMWH and fondaparinux are not permitted as procedural anticoagulants in this protocol.

Use of glycoprotein IIb/IIIa inhibitors will be at the discretion of the investigator for stable patients. Patients with biomarker positive acute coronary syndromes in whom procedural anticoagulation is achieved with unfractionated heparin should receive a procedural glycoprotein IIb/IIIa inhibitor dosed per standard of care. Glycoprotein IIb/IIIa inhibitors should not routinely be used in bivalirudin anticoagulated patients unless 1) the patient had an acute coronary syndrome and did not receive recommended pre-loading with a P2Y12 receptor inhibitor (and in whom cangrelor is not used during the PCI); and/or 2) refractory ischemic and/or thrombotic complications develop during the procedure.

7.2.4 Statin Therapy

In the absence of absolute contraindications to statin use (e.g. severe allergy with prior use), it is strongly recommended to preload with statins 12 hours prior to the procedure regardless of LDL level and history of prior or current statin use. Recommended statin loading dose regimens include atorvastatin 80 mg or rosuvastatin 40 mg.

7.3 Index Procedure

7.3.1 Baseline (Pre-Procedure) Angiography

Baseline angiography of the target vessel(s) will be completed as per the Angiographic Core Laboratory Protocol.

7.3.2 Imaging Guidance Document

The Imaging Guidance Document will provide specific details and instructions from the angiographic core laboratory regarding vessel sizing. This document will be separate from the protocol.

7.3.3 Treatment Rules of the Target Lesion(s)

Please see **Protocol Summary,** Treatment Strategy, for details of the treatment rules of target lesion(s).

7.3.4 *Treatment Rules of Unplanned Non-Target Lesion(s)*

In situations where treatment of a planned target lesion revealed additional lesion(s), the additional lesion(s) may be treated. These lesions are considered unplanned lesions. If the lesion meets enrollment criteria both before and after pre-dilatation, the lesion must be treated with the assigned device and will be considered as an unplanned target lesion. If the lesion does not meet the enrollment criteria (either before or after pre-dilatation), the lesion must be treated with XIENCE and will be considered as an unplanned non-target lesion.

7.3.5 Bailout Stenting or Alternative Procedures

Bailout procedures may be performed if the subject experiences:

- Dissection requiring intervention
- Occlusive complication as evidenced by a decrease in target vessel flow
- Chest pain or ischemic changes measured by ECG that do not respond to repeat balloon inflations, medical therapy or lytic agents
- Unplanned additional device is required to cover the target lesion

During randomization, if a bailout device is required for a target lesion (e.g., for edge dissection), the same device as the implanted device must be used. Overlap of the bailout stent/scaffold with the implanted stent/scaffold should be 1-2 mm. Gaps should be avoided.

  - o Use Absorb BVS if target lesion is treated with Absorb BVS.
  - o Use XIENCE if target lesion is treated with XIENCE.
  - o If a bailout with an Absorb BVS device cannot be delivered to the site of the lesion, the device should be carefully withdrawn and a XIENCE used.
  - o If an appropriate size Absorb BVS is not available XIENCE can be used.

IMPORTANT: It is required that the bailout device be placed so that there is no visible gap between the Absorb BVS and the bailout device. In such a case, at least 1 mm (minimum) to 2 mm (maximum) overlap is required.

IMPORTANT: In the rare event of acute occlusion following Absorb BVS placement and an additional drug-eluting stent is required for treatment, the bailout device should be XIENCE and deployed within the Absorb BVS such that the Absorb BVS is completely covered by the bailout device if this is believed to be in the best interest of the patient.

Although a bailout procedure is not considered a major adverse cardiac event (MACE) unless the subject sustains death, emergent CABG, PCI or MI, such procedures should be avoided unless required for safe subject management.

7.3.6 Final (Post-procedure) Angiography

Angiographic imaging will also be performed after the Absorb BVS or XIENCE stent deployment. Physicians should follow accepted hospital imaging practice to ensure good apposition of the Absorb BVS or XIENCE to the vessel wall. For angiographic imaging, post-implantation images should be captured the same orthogonal views that were used for the pre-procedure images (after the guidewire has been withdrawn). Intracoronary nitroglycerine should be re-administered before final angiography. If nitroglycerine is not available, intravenous nitroprusside or intravenous calcium channel blocker may be used per physician discretion.

7.3.7 Final (Post-procedure) IVUS and OCT

IVUS and OCT may be performed post-procedure per site standard of care. If stent or scaffold under-expansion or substantial malapposition is seen and post-dilatation required, a non-compliant balloon should be used. Do not dilate the Absorb BVS beyond the dilatation limit which is 0.5 mm above the nominal diameter. Repeat angiography in orthogonal views must be performed after any additional inflations.

7.4 Post–procedure

7.4.1 Post-procedure Information to be Recorded

The following information needs to be obtained between 12 hours following the index procedure and hospital discharge (in-hospital stay is considered to be a maximum of 7 days following the index procedure).

Between 12 hours post-procedure and discharge

- Date of discharge
- Antiplatelet medications
- Chronic concomitant medications
- Adverse Events, if any

7.4.2 Post-procedure Laboratory and Clinical Tests

The following laboratory assessments need to be obtained between post-index procedure and hospital discharge. Hospital discharge cannot occur prior to 16 hours to ensure complete post-procedure cardiac enzyme collection.

IMPORTANT: These tests must be performed whether or not they are considered part of the Investigator's standard of clinical practice.

Post-procedure and discharge

- A 12-lead ECG must be obtained within 24 hours post procedure.

- Both Creatine kinase (CK) and Creatine kinase myocardial-band isoenzyme (CK-MB) must be obtained for ALL subjects as it will be used for cardiac assessment of subjects post-index procedure

    - First post-procedure CK and CK-MB draw at 6 to 12 hours post-procedure.

    - Second post-procedure CK and CK-MB draw at 18-24 hours post-procedure, or at the time of discharge as long as discharge is at or after 16 hours post-procedure**.

    - If either of the post-procedure CK-MB levels are ≥ 5x ULN, serial CK and CK-MB levels must be drawn until they are falling.

** For subjects discharged prior to 16 hours, the subject will have to return to the enrolling institution for their second biomarker draw.

Alternatively, a visiting nurse may be sent to the patient's home to collect the blood sample. CK and CK-MB levels are required at all time points. Troponins are required pre-procedure and from the arterial sheath prior to first balloon inflation during the procedure in patients with acute coronary syndromes. All troponin, CK and CK-MB levels collected at any time points pre-procedure, during the procedure and post-procedure, should also be documented in the electronic case report forms.

For subjects having staged procedures, the post-procedure cardiac enzyme and 12-lead ECG assessment for the original index procedure must be repeated following the staged procedure in the same manner as done for the original index procedure.

7.4.3 Assessment of perception bias.

Patients' perception as to whether they received the control or test device may affect the rate of angina. As described in section 4.5.2, comprehensive efforts will be undertaken to maintain patient blinding. Nonetheless, for a variety of reasons patients may develop a belief as to which device they received, even if the blind is maintained.

To assess any potential perception bias on the secondary endpoint of percentage of patients who experienced angina within 1 year, information will be collected in a brief patient perception assessment questionnaire administered by the research coordinator post-procedure in the hospital prior to discharge (≥ 4 hours to ≤ 7 days after the procedure) and at 1 year. Subjects will be asked for their perception of what treatment they believe they might have received, and the basis of this perception. The following question(s) will be asked:

1. Do you think you know which treatment you have received?
    a. Yes.
    b. No.

    If answered "Yes" to Question #1, then answer the following questions. If answered "No" to Question #1, do not answer the following questions.
2. Which treatment do you think you have received?
    a. Standard metal stent.
    b. Temporary dissolving stent.
3. Are you certain?
    a. Yes.

b. No.

4. Why do you think you know?
    a. I was told by /overheard the doctor who did the procedure.
    b. I was told by/overheard another person in the procedure room/cath lab.
    c. I was told by/overheard another person in the hospital before discharge.
    d. I was told by/overheard a family member or friend who was told.
    e. I believe so because I am feeling better.
    f. I believe so because I am not feeling better.
    g. Other (write in).

7.4.4 Follow-up Antiplatelet Medications

All subjects must be maintained at a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients) or 90 mg twice daily of ticagrelor for a minimum of 12 months following the procedure. For prasugrel subjects < 60 kg in weight or ≥75 years of age, a maintenance dose of 5 mg per day for 12 months is recommended. Patients with prior stroke or TIA should receive clopidogrel or ticagrelor, and cannot be administered prasugrel. All subjects must receive between ≥75 to ≤ 100 mg of aspirin daily through 5 years follow-up during the study and should continue to take aspirin indefinitely.

Refer to respective prescribing information for P2Y12 receptor inhibitor for further details regarding maintenance dose. The start of anti-platelet medications, any changes or discontinuation of the medications, as well as the reasons for those change will be documented in the eCRF.

For subjects having staged procedures, the follow-up regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be maintained following both the original index procedure and the staged procedure.

7.4.5 Other Chronic Concomitant Medications

Please refer to **section 7.4.4** of ABSORB III Protocol (Version 17.0, August 16, 2018) for the relevant information about concomitant medications.

7.5 Clinical Follow-up for All Subjects

Please see **Protocol Summary** for clinical follow-up schedule and PRO follow-up assessments.

Registered subjects must be clinically followed even if no assigned device is implanted. Clinical follow-up visits must be conducted by a blinded physician, research coordinator, Nurse Practitioner or Physician Assistant who has been trained to the protocol.

For subjects having staged procedures, the follow-up period is considered as having begun upon completion of the original index procedure.

To assess any potential perception bias on the secondary endpoint of percentage of patients who experienced angina within 1 year, information will be collected in a brief patient perception assessment questionnaire administered by the research coordinator post-procedure in the hospital prior to discharge (≥ 4 hours to ≤ 7 days after the procedure) and at 1 year.

The PRO questionnaires will be mailed to the subject for completion or can be completed during the phone or office visit. If questionnaires are mailed to the subjects, the subjects must mail the questionnaires back to the clinical site.

The following information will be collected at each of the time points:

- Any adverse events (including re-hospitalizations)*, repeat coronary angiography, details regarding angina, medications, laboratory tests and 12-lead ECGs, if performed;
- Any angina events
    - If the subject experiences any symptoms of abnormal chest/arm/neck/jaw discomfort or pain, including angina-equivalent or atypical angina pain/sensation, data will be solicited and recorded regarding angina and angina-equivalent symptoms, including the quality, frequency and severity of discomfort/pain, to allow the CEC to adjudicate the symptoms as to angina/angina-equivalent vs. non-angina. This information will be collected by the research coordinator using a standard script. A blinded cardiologist will review the information collected by the research coordinator, provide a diagnosis and sign-off on his/her diagnosis.
- Any repeat coronary angiography and results of such, if applicable;
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG);
- Use and compliance of medications per clinical investigation plan;
- Use and changes in concomitant cardiovascular medications.

* All adverse events must be collected up to and including to the 1 year follow up for all ~2600 subjects. Following the 1-year follow-up, it is mandatory to collect information on cardiac adverse events, device related adverse events and on serious adverse events. Please see **section 8.3.1** for details on adverse event reporting.

7.6 Additional Follow-up Visits for All Subjects

Additional subject visits, such as unscheduled visits, may occur as clinically warranted. The following information will be collected:

- Assessment of angina status
- Adverse events (including re-hospitalizations)
- Repeat coronary angiography
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Use and compliance to protocol medications (aspirin and prasugrel/clopidogrel/ ticagrelor/ticlopidine)

- Use and changes in chronic concomitant medications (Refer to **Appendix II** for definition)

For unscheduled visits for suspected ischemic cardiac events, sites should make reasonable efforts to obtain cardiac enzymes (Troponin I or T), CK and CK-MB, and/or ECG if the site is aware of the visit at the time of its occurrence. In all other scenarios (i.e., site does not become aware until after the fact), no protocol deviation will be issued if Troponin I or T, CK and CK-MB, and/or ECG were not obtained at the time of the unscheduled visit.

All efforts must be made to obtain follow-up information on subjects who have undergone procedures or have been treated for adverse events in a non-trial-related hospital(s).

All coronary revascularizations must be classified prospectively by the investigator as ischemia-driven or not ischemia-driven (Refer to **Appendix II** for definition). If a subject has a coronary revascularization, all clinical information such as symptoms or lack of symptoms of ischemia, and possible relations with the target lesion/vessel should be fully recorded in the source documents prior to angiogram.

8. ADVERSE EVENTS

8.1 Definitions

To comply with worldwide standards and guidelines on clinical trial adverse event reporting, AV has developed the below definitions to be used and adhered to by the investigators. The exact definitions as referenced in these standards and guidelines are included in appendix II.

8.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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

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

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health that either:

1) Resulted in a life-threatening illness or injury, or

2) Resulted in a permanent impairment of a body structure or a body function, or

3) Required in-patient hospitalization or prolongation of existing hospitalization, or

4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

8.1.3 Device Deficiency/Product Experience

Device deficiency (DD) is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

Product Experience (PE) is defined as any expression of customer concern or dissatisfaction, including adverse events and patient issues that occurred during or after the use of a commercially available medical device.

8.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate eCRF form. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease and presence (or absence) of a more-likely cause.

8.2.1 Unanticipated Serious Adverse Device Effect (USADE)

Unanticipated serious adverse device effect (USADE) refers to 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.

8.3 Adverse Event/ Device Deficiency/ Product Experience Reporting

8.3.1 Adverse Event and Serious Adverse Event Reporting

All adverse events will be collected on each subject through the 1-year follow-up visit. After one year, only the following will be collected:

- All serious adverse events.
- All cardiac events regardless of seriousness or device relationship.
- All trial device-related events and events for which the relationship to the trial device is unknown.
- All unanticipated adverse device effects.
- All Cerebral Vascular Accidents (CVAs).

The Investigator will monitor the occurrence of adverse events for each registered subject during the course of the clinical trial/investigation and report as required by this protocol in section 8 per AE and SAE definitions. Adverse Events reported by the subject, observed by the Investigator, or documented in medical records should be recorded on the adverse event eCRF, whether believed by the Investigator to be related or unrelated to the investigational device implant as required by this protocol.

A fax form will be made available to allow the investigator to report SAEs and device deficiencies in the event the entry cannot be made in the EDC (FRM2073001 SAE Notification Form). This does not replace the EDC reporting system, however, all information must still be entered in the EDC system as soon as feasible.

For all registered patients, AEs (any new event/experience that was not present at baseline or worsening of an event present at baseline) will be collected as required by this protocol. The reporting of AEs will start when the guiding catheter enters the subject's vasculature. Reported AEs will be monitored through the course of the trial. Additional information with regards to an AE should be updated within the appropriate case report form.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be recorded on the AE eCRF page.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Study site	**Reporting timelines**

All Study Sites	SAEs must be reported no later than 3 calendar days from the day the study personnel becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The date the site staff became aware that the event met the criteria of a serious adverse event must be recorded in the source document. The investigator will further report the event to the IRB/EC according to the institution's IRB/EC reporting requirements.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system. However they need to be reported on the SAE Notification Form (FRM2073001).

Serious adverse events should be reported on the SAE Notification Form in the occurrence that the EDC System is not available. This does not replace the EDC reporting system. All information must still be entered in the EDC system once the system is back to normal function.

8.3.2. Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

Abbott Vascular requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements

8.3.3 Device Deficiency/Product Experience Reporting

All device deficiencies/product experiences should be reported within the EDC System on the appropriate eCRF. A fax form will be made available to allow the investigator to report device deficiencies in the event that the entry cannot be made in the EDC (Device Deficiency Report Form). This does not replace the EDC reporting system. However, all information must still be entered in the EDC system as soon as feasible. In case a device deficiency occurred before the patient ID and randomization number has been assigned, the device deficiency should be reported to the sponsor via a Device Deficiency Report Form.

The investigator should report all DDs/PEs to the Sponsor as soon as possible but no later than outlined below.

Study sites	**Reporting timelines**
All Study Sites	DDs/PEs must be reported no later than 3 calendar days from the day the study personnel becoming aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined.

The device, if not implanted or not remained in the subject, should be returned to Abbott Vascular.

Device deficiencies should be reported to the IRB/EC per the investigative site's local requirements.

8.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report the SAEs and DDs/PEs to the country regulatory authority, per local requirements.

8.4 Safety Monitoring by Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will serve in an advisory role to Abbott Vascular to ensure safety by reviewing cumulative data from the clinical trial at pre-scribed intervals for the purpose of safeguarding the interests of trial participants. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB charter. Based on safety data, the DSMB may consider a recommendation for modifications or termination of the trial based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to trial modifications rest with Abbott Vascular.

9. ADJUDICATION OF EVENTS

9.1 The Clinical Events Committee (CEC)

Please refer to **section 9.1** of ABSORB III Protocol (Version 17.0, August 16, 2018) for relevant information on CEC. In addition to the events adjudicated in ABSORB III, in ABSORB IV the CEC will also adjudicate any patient reported symptoms of abnormal chest/arm/neck/jaw discomfort or pain to angina/angina-equivalent vs. non-anginal symptoms.

9.2 Angiographic Core Laboratory

The angiographic core laboratory will be responsible for reviewing all available follow-up coronary angiograms for registered subjects, to determine if a revascularization was performed by PCI, and if so, whether or not the revascularization was related to the target lesion, target vessel or non-target vessel. The angiographic core laboratory will also assess the initial completeness of revascularization as previously described.[57,58] The data from angiographic core laboratory will be provided to CEC for adjudicate stent thrombosis events with angiographic follow-up.

10. STATISTICAL ANALYSIS

10.1 Statistical Overview

The sample size was originally based on a powered landmark analysis. The powered landmark analysis has since been removed, however, the sample size was sufficient to support the testing of the powered 30 day TLF primary endpoint and the powered secondary endpoints of 1 year TLF and 1 year angina. TLF is defined as a per-subject hierarchical count of cardiac death, target vessel Q-wave or non-Q-wave MI (per protocol-defined MI definition, Appendix II), or ischemia-driven target lesion revascularization (ID-TLR).

[57] Rosner GF et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial". *Circulation.* 2012;125:2613-2620

[58] Genereux P et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention. The residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol. 2012 Jun 12;59(24):2165-74

Details on the design of this endpoint will be included when finalized.

Study Success

Study success is defined as passing the non-inferiority test of Absorb BVS to XIENCE on the Primary Endpoint of TLF through 30 days.

10.2 Analysis Populations

10.2.1 Intent-to-Treat (ITT) Population

The ITT population is defined as the subjects registered in the study at the point of randomization, regardless of the treatment actually received. Subjects will be analyzed in the treatment group to which they were randomized. Subjects enrolled but not randomized will not be included in the ITT population.

10.2.2 As-Treated (AT) Population

The As-Treated (AT) population will consist of subjects who were randomized and have received at least one study device (Absorb BVS or XIENCE) at the target lesion. Subjects who have received at least one Absorb BVS device will be included in the Absorb BVS arm; and subjects who have received at least one XIENCE device and none of Absorb BVS device will be included in the XIENCE arm.

10.3.1 ABSORB IV Primary Endpoint

Primary Endpoint: TLF at 30-day Primary Endpoint

TLF at 30-day will be tested for non-inferiority. This analysis will consist of ~2600 subjects in ABSORB IV.

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the TLF at 30 days with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{TLF}$

H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{TLF.}$

TLF_{BVS} and TLF_{XIENCE} are the 30-Day TLF rates in the Absorb BVS and XIENCE arms, respectively. Δ_{TLF} is the non-inferiority margin for this powered primary endpoint.

The power calculation for the primary endpoint of TLF at 30 days is based on the following assumptions:

- The true 30-Day TLF rate is assumed to be 4.9% for both the Absorb BVS arm and the XIENCE arm
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 2.9%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)

- 1% loss to follow-up at 30 days

  With the effective sample size 2574 (Absorb: 1287, XIENCE: 1287) at 30 days, the study has approximately 92% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test.

10.3.2 Powered Secondary Endpoints

Powered Secondary Endpoint 1: TLF through 1 year

TLF at 1-year will be tested for non-inferiority. This analysis will consist of ~2600 subjects in ABSORB IV.

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for the TLF at 1 year with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $TLF_{Absorb} - TLF_{XIENCE} \geq \Delta_{TLF}$

H_A: $TLF_{Absorb} - TLF_{XIENCE} < \Delta_{TLF.}$

TLF_{Abosrb} and TLF_{XIENCE} are the 1 year TLF rates in the Absorb BVS and XIENCE arms, respectively. Δ_{TLF} is the non-inferiority margin for this powered secondary endpoint.

The power calculation for the secondary endpoint of TLF at 1 year is based on the following assumptions:

- The true 1 year TLF rate is assumed to be 9.7% for both the Absorb BVS arm and the XIENCE arm.
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{TLF}): 4.8%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)
- 5% loss to follow-up at 1 year

With the effective sample size 2470 (Absorb BVS: 1235, XIENCE: 1235) at 1 year, the study has approximately 98% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test.

Power Secondary Endpoint 2: Angina through 1 year

The Angina Powered Secondary Endpoint of percentage of patients who had angina within 1 year (excluding an angina blanking period of the index hospitalization or the first 7 days post PCI, whichever occurs first) will be tested for non-inferiority with reflex testing to superiority. This analysis will consist of ~2600 subjects in ABSORB IV.

The hypothesis test is designed to show non-inferiority of Absorb BVS to XIENCE for angina within 1 year with a one-sided alpha of 0.025. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $ANGINA_{Absorb} - ANGINA_{XIENCE} \geq \Delta_{ANGINA}$

H_A: $ANGINA_{Absorb}$ - $ANGINA_{XIENCE} < \Delta_{ANGINA}$.

$ANGINA_{Absorb}$ and $ANGINA_{XIENCE}$ are the percentage of patients with angina within 1 year in the Absorb BVS and XIENCE arms, respectively. Δ_{ANGINA} is the non-inferiority margin for this secondary endpoint.

The power calculation for the Angina Secondary Endpoint within 1 year is based on the following assumptions:

- The true percentage of patients with angina within 1 year is assumed to be 22.6% for both the Absorb BVS arm and the XIENCE arm
- One-sided alpha: 2.5%
- Non-inferiority margin (Δ_{ANGINA}): 7%
- Randomization ratio (ABSORB IV): 1 (Absorb BVS arm) : 1 (XIENCE arm)
- 5% loss to follow-up at 1 year

With the effective sample size 2470 (Absorb: 1235, XIENCE: 1235) at 1 year, the study has approximately 99% power to demonstrate non-inferiority of Absorb BVS to XIENCE using Farrington and Manning test.

If the non-inferiority of Absorb BVS to XIENCE is demonstrated and the percentage is lower in Absorb BVS compared to XIENCE, a superiority test will be performed at the two sided alpha 0.05 level.

The null (H_0) and alternative (H_A) hypotheses are:

H_0: $ANGINA_{Absorb}$ - $ANGINA_{XIENCE} = 0$

H_A: $ANGINA_{Absorb}$ - $ANGINA_{XIENCE} \neq 0$

$ANGINA_{Absorb}$ and $ANGINA_{XIENCE}$ are the percentage of patients with angina within 1 year in the Absorb BVS and XIENCE arms, respectively.

With the effective sample size 2470 at 1 year, the study has approximately 86% power to demonstrate superiority with a difference of 4.9% between the Absorb BVS arm and the XIENCE arm (e.g. 17.7% in the Absorb BVS arm vs. 22.6% in the XIENCE arm) using Pearson's Chi-square test.

The sample size calculations were performed using NCSS PASS 11 (Hintze, J., 2011, NCSS, LLC. Kaysville, Utah).

10.4 Statistical Analyses

For binary variables such as TLF, TLR, and clinical procedure success, counts, percentages, and 95% confidence intervals will be calculated, and p-values may be presented for hypothesis generating purposes. Pearson's Chi-squared test or Fisher's exact test will be performed when

appropriate. In addition, logistic regression will be performed to determine whether the baseline characteristics exhibit any trends in predicting TLF.

For continuous variables such as age, means, standard deviations, and 95% confidence intervals for the mean will be calculated and p-values may be presented for hypothesis generating purposes. For time-to-event variables, such as time to TLF, survival curves will be constructed using Kaplan-Meier estimates, and log rank test results may be displayed. Unless specified, analyses will be performed with pooled data across all study sites.

For further details refer to the statistical analysis plan (SAP).

10.4.1 Primary Endpoint Analyses

The ABSORB IV Primary Endpoint of TLF at 30-day will be analyzed for the ITT (~2600 subjects of ABSORB IV) and the AT populations. The primary analysis will be based on the ITT population. The non-inferiority hypothesis testing will be performed using non-inferiority test by Farrington and Manning. Non-inferiority of Absorb BVS to XIENCE will be established if the p-value for the non-inferiority test is less than 0.025.

Details of the analyses for the primary endpoints can be found in the statistical analysis plan (SAP).

10.4.2 Powered Secondary Endpoint Analysis

The ABSORB IV Secondary Endpoint of TLF at 1-year will be analyzed for the ITT (~2600 subjects of ABSORB IV) and the AT populations. The primary analysis will be based on the ITT population. The non-inferiority hypothesis testing will be performed using non-inferiority test by Farrington and Manning. Non-inferiority of Absorb BVS to XIENCE will be established if the p-value for the non-inferiority test is less than 0.025.

Analysis of the Angina Powered Secondary Endpoint of the percentage of patients with angina within 1 year will be based on the ITT population (~2600 subjects of ABSORB IV) and the AT population. The primary analysis will be based on the ITT population. The non-inferiority hypothesis testing will be performed using non-inferiority test by Farrington and Manning. Non-inferiority of Absorb BVS to XIENCE will be established if the p-value for the non-inferiority test is less than 0.025.

If the non-inferiority of Absorb BVS to XIENCE is demonstrated and the percentage is lower in Absorb BVS compared to XIENCE, a superiority test will be performed at the two-sided alpha 0.05 level.

10.4.3 Secondary Endpoint Analyses

Secondary endpoints other than the powered endpoints described above will be summarized descriptively for the ITT population (~2600 subjects of ABSORB IV). For further details refer to the statistical analysis plan (SAP).

10.4.4 Additional Analyses

Adverse Events related to stent/scaffold thrombosis, vascular complications or bleeding complications, and their relation with antiplatelet therapies used in the trial will be investigated between the two treatment groups, if applicable.

For further details refer to the SAP.

10.4.5 Informational Endpoint Analyses

Details on informational endpoint analyses can be found in the SAP.

10.4.6 Subgroup Analysis

Pre-specified subgroups such as diabetes, sex, age will be examined. Further details can be found in the SAP.

10.4.7 Criteria for Early Termination of the Trial for Effectiveness

No formal statistical rule for early termination of the trial for effectiveness is defined.

10.4.10 Procedures for Accounting for Missing, Unused or Spurious Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the final report.

10.4.11 Pooling Strategy

Details on pooling strategy can be found in the SAP.

10.4.12 Deviations from the Original Statistical Plan

Any major changes to the statistical plan (available upon request) will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

11. ADDITIONAL PROTOCOL INFORMATION

Please refer to **section 11 - 17** of ABSORB III Protocol (Version 16.0, March 14, 2017) for relevant information on data access and handling, quality control, ethical consideration, publication policy, risk analysis and special population.

11.1 Direct Access to Source Data/Documents Addendum

It is possible that during the duration of the trial, subjects may receive medical care from institutions other than the study site. In addition to collecting the informed consent from patients, the Sponsor strongly recommends that study sites obtain a medical release authorization from the subject to facilitate the collection of relevant medical information from non-study site institutions.

12. ABSORB-RESOLVE: REDUCTION IN ISCHEMIA WITH BIORESORBALE VASCULAR SCAFFOLDS—AN IMAGING SUB-STUDY TO ABSORB IV

12.1. Background

To date, no randomized controlled trial (RCT) has demonstrated the superiority of percutaneous coronary intervention (PCI) over medical therapy for the reduction of death or myocardial infarction (MI) in patients with stable coronary artery disease (CAD) **[1,2]**. Limitations of prior studies, however, have included excessively high rates of revascularization failure and incomplete coronary revascularization after PCI, and use of older generation stent technology (for example, only 2.7% of the COURAGE trial PCI patients received drug-eluting stents) **[1,3]**.

Despite its negative primary clinical events outcome, COURAGE and numerous other RCTs have demonstrated that angina frequency and quality of life are significantly improved with PCI over medical therapy alone **[4]**. In COURAGE, a longitudinal assessment at 24 months observed PCI to improve health status compared to medical therapy, with two-thirds of patients undergoing PCI free of angina. The most prominent effect of PCI was noted for patients with either severe or frequent angina. Importantly, approximately half of subjects enrolled into the COURAGE study were asymptomatic or experienced minimal angina for a generally short duration of ~5 months, and PCI would be expected to be more effective in a more symptomatic group.

The symptomatic improvements with PCI in the COURAGE trial—despite the low utilization of drug-eluting stents—may be mechanistically explained by the COURAGE nuclear sub-study in which myocardial ischemia was evaluated by single photon emission computed tomography (SPECT) **[5]**. Abnormal single photon emission computed tomography (SPECT) findings have been strongly associated with adverse prognosis and worsened angina **[6]**. In the COURAGE nuclear sub-study, it was hypothesized that ischemia reduction would be greater for patients who were randomized to receive PCI over those receiving medical therapy alone **[5]**. Among 309 patients who underwent baseline and follow-up stress testing by SPECT, follow-up ischemia was assessed at 6-18 months (median 12 months). In PCI-treated patients, the mean amount of ischemic myocardium was reduced from 8.2% at baseline to 5.5% at follow-up-- equating to a mean reduction of 2.7% -- which compared favorably to the mean 0.5% reduction that was observed in the medical therapy alone arm ($p < 0.001$). These findings are in direct accordance with several pivotal randomized trials including the Asymptomatic Cardiac Ischemia Pilot (ACIP) and SWISSI II studies, each of which demonstrated superior clinical outcomes with PCI compared to medical therapy alone in patients with documented ischemia **[7-8]**.

12.1.1. Ischemia Assessment by SPECT

Numerous non-invasive imaging tests exist for physiologic assessment of CAD, including echocardiography, cardiac magnetic resonance and myocardial perfusion imaging by either SPECT or positron emission tomography (PET) **[9,10]**. These modalities identify stress-induced wall motion abnormalities or regional myocardial perfusion defects as a surrogate for ischemia, and serve to identify individuals who may have severe coronary stenoses. Among the non-invasive stress modalities, myocardial perfusion imaging (MPI) by SPECT is performed most commonly, comprising ~90% of the more than 10 million stress imaging test performed in the

US annually **[11]**. MPI by SPECT determines the extent, severity and reversibility of myocardial ischemia with high performance **[12]**. In pooled analyses, the sensitivity and specificity of MPI to diagnose coronary stenosis is 85-90% and 70-75%, respectively. Further, the prognostic value of MPI is unsurpassed by other non-invasive tests, with risk of CAD events escalating exponentially with increasing magnitude of inducible hypoperfusion **[6]**.

12.1.2. Coronary CT Angiography (CCTA)

A major goal of imaging is to accurately evaluate the angiographic severity of luminal stenoses. Coronary CT angiography (CCTA) has recently emerged as an accurate non-invasive method for determination of obstructive CAD **[13]**. In three prospective multicenter studies, the diagnostic sensitivity of CCTA for patients with and without known CAD has ranged between 85-99%, with specificities ranging between 64-90% **[14-16]**. CCTA has been demonstrated to be particularly effective in excluding obstructive coronary stenosis and a normal CCTA is associated with a very low annual mortality rate of 0.13% **[17]**.

However, there are limitations of CCTA, particularly as it relates to intracoronary stents **[18]**. Owing to blooming artifacts caused by metal, visualization of the coronary lumen within stents by CCTA is more challenging than evaluation of the native coronary arteries. Clinical studies published so far show low sensitivity to identify in-stent restenosis. The limited spatial resolution of CCTA, the type of stent, and stent diameter all contribute to limited clinical results.

Importantly, as blooming artifacts are absent in CCTA imaging of bioresorbable vascular scaffolds (Absorb BVS), the diagnostic performance of CCTA may be improved after Absorb BVS implantation **[19]**. The coupling of a non-invasive technique for evaluation of symptomatic or ischemic patients with suspected in-scaffold restenosis may be cost-effective compared to traditional evaluation of metallic stents **[20]**.

12.1.3. CT Perfusion (CTP)

Recent advances in technology now enable MPI by CT, a procedure termed CT perfusion (CTP) **[21].** Multidetector CT systems can image in a dynamic mode, in which sequential images are obtained over a period of time to record the kinetics of iodinated contrast in the arterial blood pool and myocardium. George et al, using a 64-detector CT in a canine ischemia model, performed CTP during adenosine infusion **[22]**. They found strong correlations between the ratio of myocardial upslope and left ventricular upslope and microsphere-derived MBF. The authors replicated the study in humans with adenosine stress 64- and 256-row detector CCTA and CTP. In the human study, they calculated the transmural perfusion ratio (sub-endocardial attenuation / sub-epicardial attenuation), which had a significant inverse linear correlation with percent diameter stenosis on quantitative intracoronary angiography (ICA) **[23]**. Further, the combination of CTP and CCTA was 86% sensitive and 92% specific for identifying patients with atherosclerosis causing perfusion abnormalities when compared with the combination of ICA and SPECT-MPI as the gold standard.

In a prospective multicenter study of chest pain patients entitled the Combined Coronary Atherosclerosis and Myocardial Perfusion Evaluation Using 320 Detector Row Computed Tomography (CORE320) **[24]**, CCTA with concomitant CTP was as effective as sequential SPECT-MPI and invasive angiography in identifying flow-limiting atherosclerotic lesions. The clinical utility of CTP may be particularly important in patients with a high coronary risk profile, known coronary artery disease, those with a high calcium score (e.g. >400 Agatston Units), or

those with suspected in-stent restenosis in whom severe coronary calcification or artifacts prevent accurate quantification of coronary stenosis by CT angiography. In patients scheduled for percutaneous revascularization, information about both coronary lesion characteristics and myocardial segments with reversible ischemia or infarcts may be helpful to plan the procedure and provide prognostic information.

12.1.4. FFR_{CT}

At present, the "gold" standard assessment of the hemodynamic significance of coronary stenoses is fractional flow reserve (FFR). Recent advances in computational fluid dynamics (CFD) allow for calculation of coronary flow and pressure fields from anatomic image data **[25]**. Applied to CT, these technologies enable calculation of FFR (which reflects the ratio of maximal myocardial blood flow through a diseased artery to the blood flow in the hypothetical case that the artery was normal) without additional imaging or administration of additional medications. Several studies have reported incremental value of FFR_{CT} in the diagnosis of CAD **[26-28]**. In the most contemporary of these prospective multicenter trials, the HeartFlowNXT study of 254 patients with suspected CAD, FFR_{CT} was more accurate for identification of ischemia-related arterial blockages than standard CCTA or ICA. Perhaps more importantly, FFR_{CT} data matched closely with invasively measured FFR. The area under the receiver operating characteristic curve (AUC) was 0.82 for FFR_{CT} ($\leq$ 0.80) vs. 0.63 for CCTA (lumen reduction > 50%) ($p < 0.0001$) with invasive FFR as the reference standard. Per-patient sensitivity and specificity were 86% and 79% for FFR_{CT} vs. 94% and 34% for CCTA, and 91% and 51% for ICA (lumen reduction >50%).

FFR_{CT} offers several practical advantages in that it does not require modification of CT angiography protocols, does not require administration of additional medications beyond what is typically administered for CCTA, and does not result in any additional radiation exposure.

12.1.5. The Present Study

In the present proposal, we propose to determine the effects of the Absorb BVS on reversible myocardial and coronary lesion-specific ischemia by SPECT, CTP, and FFR_{CT}; and to quantify group-to-group differences in myocardial ischemia in individuals undergoing coronary intervention with bioabsorbable scaffolds versus latest generation drug-eluting stents. Further, we will evaluate the long-term vascular responses to Absorb BVS by traditional diagnostic coronary CT angiography.

The first subject for the RESOLVe study was enrolled on February 15, 2015. Enrollment in ABSORB-RESOLVe has been challenging and as of January 11, 2017, only 16 subjects, out of the 370 planned, have been enrolled. Therefore, due to this very slow enrollment, this sub-study has been stopped and will no longer enroll patients. For patients already enrolled, clinical follow-up will continue as per protocol; however subjects will not undergo the ABSORB-RESOLVe specific testing specified in the protocol.

12.2. Rationale and Design of ABSORB-RESOLVe

Hypothesis-generating clinical observations have surfaced that Absorb BVS may result in less angina than XIENCE. Specifically, the site-reported recurrence rate of angina after PCI was compared at different time periods from the SPIRIT IV trial (n = 2,051) and the ABSORB EXTEND registry (n = 375) (data on file, Abbott Vascular). Of note, both studies evaluated

angina recurrence at similar intervals and with similarly designed case report forms. This comparison excluded complex patients and lesions from SPIRIT IV (3-vessel PCI; PCI of 2 lesions in a single vessel; RCA aorto-ostial lesions; bifurcation lesions). Non-Japanese Asian patients from ABSORB EXTEND were excluded because of historically low reported event rates and for more appropriate comparison to patients in SPIRIT IV. At 30 days angina had recurred in 12.5% of XIENCE patients vs. 5.8% of Absorb BVS patients. At 1 year angina had recurred in 26.7% of XIENCE patients vs. 15.9% of Absorb BVS patients (393 day HR [95% CI] = 0.55 [0.42, 0.72], $p < 0.0001$). To further correct for baseline differences, a propensity adjusted comparison was performed between 602 XIENCE patients and 287 Absorb BVS patients (data on file, Abbott Vascular). In this analysis angina at 30 days had recurred in 11.3% of XIENCE patients vs. 7.0% of Absorb BVS patients. At 1 year angina had recurred in 28.1% of XIENCE patients vs. 16.0% of Absorb BVS patients (393 day HR [95% CI] = 0.53 [0.93, 0.74], $p = 0.0001$). It is unknown to which extent this reduction in angina recurrence is due to reduced ischemia with Absorb BVS compared to XIENCE.

The ABSORB-RESOLVe sub-study of the parent ABSORB IV trial has been specifically designed to address each important stage and mechanism of the ischemic cascade wherein the Absorb BVS may exert salutary anti-anginal effects. The substudy will employ both SPECT and CT in patients undergoing a prospective, multicenter, randomized 1:1 comparison of Absorb BVS to XIENCE.

SPECT will be performed for determination of changes in myocardial ischemia. SPECT is currently the most commonly performed and most well-validated stress imaging test available, and enables quantification of relative perfusion deficits within myocardial territories, findings that can arise from both epicardial coronary artery (re-)stenosis as well as microcirculatory dysfunction and/or disease. Additionally, the evaluation of functional capacity through exercise testing in those who are capable of it will allow for a direct assessment of the potential beneficial effects of Absorb BVS on reducing exertional angina. Available SPECT images taken within 60 days prior to the index procedure will be analyzed to obtain a baseline measurement of ischemia. SPECT will be performed at 14 months, a time period after which most restenosis events have occurred, and a time period in which non-randomized comparative data have suggested that Absorb BVS implantation is associated with substantially less angina than the XIENCE metallic DES, the hypothesis which is being formally tested in ABSORB III. Finally, ischemia will be provoked prior to SPECT with a Bruce exercise test. Ischemia provoked by exercise is inherently different than pharmacologic induced differences in blood flow, and the inherent differences in vascular responses after Absorb BVS compared to XIENCE V (including exercise induced vasodilation at the treatment site and restored cyclic pulsatility) may be optimally differentiated with exercise induced hemodynamic changes. Exercise testing also allows between-group comparisons of additional variables including exercise time/capacity and ECG changes, and exercise induced angina.

CT—inclusive of coronary CT angiography, CT perfusion, and FFR_{CT}—will be performed at baseline, after the device has been implanted, and at 5-year follow-up for determination of changes in myocardial and coronary ischemia after Absorb BVS absorption is complete. CT will allow for assessment of the presence, extent and severity of coronary luminal stenosis, which are directly associated with ischemia and adverse events. Further, CT also allows for performance of pharmacologic CTP and FFR_{CT}. Both of these tests are "disruptive" methods for CAD evaluation. Given the spatial resolution of CT, MPI by CTP offers a distinct advantage over SPECT for evaluation of sub-endocardial ischemia evaluation while FFR_{CT} allows for

determination of epicardial coronary lesion-specific ischemia. The baseline CT will allow determination of residual ischemia present in each group immediately after the procedural implant, whether originating from the target vessel or non-target vessel territories. Such residual ischemia will be correlated with early onset angina in each treatment group. The 5-year follow-up CT, a time period in which the Absorb BVS has completely resorbed, allowing vascular remodeling with late lumen enlargement as well as restoration of normal vasomotion, will provide the highest likelihood of determining whether Absorb BVS reduces ischemia compared to XIENCE during long-term follow-up, consistent with the hypothesis which is being formally tested in ABSORB IV. In addition, CT at 5-years will be able to characterize changes in plaque morphology and extent and vessel dimensions and remodeling after resorption of the Absorb BVS, and correlate such changes to long-term outcomes in the 2 groups.

12.3. ABSORB-RESOLVe Study Objectives:

12.3.1. Primary Objective (Myocardial Ischemia by SPECT).

The primary powered objective is to compare the efficacy of between group differences in % ischemic myocardium after treatment with Absorb BVS versus XIENCE at 14 ± 1 month follow-up, as evaluated by SPECT. Percent (%) ischemic myocardium will be based upon a summed stress score (SSS), which will be calculated for all myocardial segments using a 17-segment AHA model. Each segment will be classified as having normal myocardial perfusion (=0), mild perfusion defect (=1), moderate perfusion defect (=2), severe perfusion defect (=3), or absence of perfusion (=4). The SSS will be converted as a function of 100, resulting in per-subject % ischemic myocardium.

Sample Size Calculation. For the between-group analysis using SPECT, an *a priori* power analysis was performed to test the hypothesis that implantation of Absorb BVS will be associated with lower per-subject % ischemic myocardium, compared to XIENCE stents at 14 ± 1 month follow-up.

In the present study, for estimated % ischemic myocardium, we utilized per-patient data from the COURAGE nuclear substudy where PCI + OMT therapy resulted in 5.5% ± 5.1% residual % ischemic myocardium at 6-18 month follow-up. Given the uniformity of use of the XIENCE drug-eluting stents in the ABSORB IV trial that was not present in the COURAGE study, we anticipate a lower residual % ischemic myocardium in ABSORB RESOLVe than was observed in COURAGE, and have estimated this to be an ~25% relative improvement, or 4.0% ± 3.7%.

Based upon a 14 ± 1 month per-patient % ischemic myocardium of 4.0% ± 3.7% for XIENCE, we assume a 2.7% ± 3.7% per-patient % ischemic myocardium for Absorb BVS, i.e. a 33% relative reduction. This 33% reduction is a conservative estimate based on the 47% observed reduction in angina at 1 year in the propensity adjusted comparison of Absorb BVS vs. XIENCE described in section 12.2 above. With 370 total subjects (185 per group), employing a 2-sided alpha = 0.05, and assuming 5% of patients are lost to follow-up, the statistical power will be 90%.

12.3.2. Powered Secondary Objective (Myocardial Ischemia by CT).

The secondary powered objective is to compare the efficacy of between-group differences in % ischemic myocardium after treatment with Absorb BVS versus XIENCE at 62 ± 1 month follow-

up as evaluated by CT perfusion. Percent (%) ischemic myocardium will be based upon a summed stress score in a manner identical to that for SPECT.

Sample Size Calculation. For the between-group analysis using CT perfusion at 62 ± 1 month, there are no long-term myocardial perfusion studies after PCI on which to base estimates of % ischemic myocardium. However, given the durability of long-term freedom from re-intervention observed for both Absorb BVS and XIENCE **[29-31]**, it is reasonable to employ the same assumptions as used for the primary endpoint for SPECT in accordance with the COURAGE study. Based upon a per-patient % ischemic myocardium of 4.0% ± 3.7% for XIENCE, we assume a 2.7% ± 3.7% per-patient % ischemic myocardium for Absorb BVS, i.e. a 33% relative reduction. We further assume a non-evaluable CT perfusion study rate at 62 ± 1 month of 10%. With 370 total subjects (185 per group), and employing a 2-sided alpha = 0.05, the statistical power will be 83%.

12.3.3. Tertiary Objectives:

12.3.3.1. Myocardial Ischemia by SPECT.

To compare the effect of revascularization by Absorb BVS versus XIENCE on additional measures of between-group reversible ischemia differences at 14 ± 1 month follow-up. For this tertiary objective, myocardial ischemia will be evaluated by SPECT. Myocardial ischemia measures will include:

1) Per-vessel territory % ischemic myocardium. Vessel territories will include those from the left anterior descending artery, left circumflex artery and right coronary artery.

2) Significant ischemia reduction, as defined by ≥ 5% ischemic myocardium

3) Rates of myocardial perfusion normalization

4) Rates of residual ≥10% ischemic myocardium

5) Reduction in high-risk SPECT findings (e.g., transient ischemic dilatation, increased lung uptake, right ventricular dilatation)

6) Exercise-induced angina

7) Exercise duration

8) ST-segment depression during exercise

9) Improvement in Duke Treadmill Score

12.3.3.2. Myocardial Ischemia by SPECT

To assess the reduction in % ischemic myocardium in ABSORB RESOLVe sub-study subjects from pre-procedure to 14 ± 1 month follow-up, and to assess between-group differences in the reduction of % ischemic myocardium between the Absorb BVS and XIENCE arms. Baseline SPECT imaging is not mandated per protocol; this secondary analysis will be performed only on subjects who have an available non-study SPECT and will be used for determination of reduction in % ischemia myocardium from pre-procedure to 14 ± 1 month follow-up.

12.3.3.3. Myocardial Ischemia by SPECT

To assess the extent of myocardial ischemia in ABSORB RESOLVe sub-study subjects who have met the parent ABSORB IV angina secondary endpoint (angina group) in comparison to subjects who have not met the angina secondary endpoint (non-angina group), and to assess between-group differences in the Absorb BVS and XIENCE arms. ABSORB IV angina secondary endpoint is defined in **Section 5.2** of the ABSORB IV portion of the protocol.

12.3.3.4. Myocardial Ischemia by CT.

To compare the effect of revascularization by Absorb BVS versus XIENCE on additional measures of reversible ischemia reduction in a) the immediate post PCI period (within 7 days after the index PCI procedure) and b) at 62 ± 1 month follow-up. For this tertiary objective, myocardial ischemia (for both the target vessel territory and global ischemia) will be evaluated by CT perfusion. Myocardial ischemia measures will include:

1) Between group reversible myocardial ischemia at 7 days.

2) Within-patient reversible myocardial ischemia change from 7 days to 62 ± 1 month follow-up.

3) Rates of myocardial perfusion normalization.

4) Reduction in reversible myocardial ischemia by severity class [as classified by none (0%), mild (1-4%), moderate (5-9%) and severe (≥ 10%) ischemic myocardium.

5) Rates of residual ≥ 10% ischemic myocardium.

12.3.3.5. Lesion-Specific Ischemia by CT.

To compare the effect of revascularization by Absorb BVS versus XIENCE on measures of target vessel and lesion-specific ischemia reduction in a) the immediate post PCI period (within 7 days after the PCI period) and b) at 62 ± 1 month follow-up. For this tertiary objective(s), target vessel and lesion-specific ischemia will be evaluated by FFR_{CT}. Lesion-specific ischemia measures will include between group (at 7 days and at 62 ± 1 month follow-up) and within – patient (change from 7 days to 62 ± 1 month follow-up):

1) Differences in absolute FFR_{CT} value.

2) Rate of trans-lesion hyperemic pressure difference normalization (as defined by $FFR_{CT} \geq 0.80$).

12.4. ABSORB-RESOLVe Study Population and Clinical Site Participation

The study populations will consist of 370 consecutive consenting adult patients registered in the parent ABSORB IV trial. Site participation will be voluntary. The ABSORB-RESOLVe and parent ABSORB IV study subject enrollment will be simultaneous; that is, the 370 subjects registered in this sub-study will be a part of the ~2600 subjects in the ABSORB IV trial. These subjects will undergo all ABSORB IV scheduled follow-up and assessments in addition to the tests associated with this sub-study.

12.4.1. Selection of Subjects

12.4.1.1. Inclusion Criteria (in addition to standard inclusion criteria from ABSORB IV parent trial):

1) Subjects that received only Absorb BVS or XIENCE as per their assigned treatment group.

2) Successful and uncomplicated PCI procedure, as defined in the main protocol.

3) Provision of informed, written consent for the ischemia substudy.

12.4.1.2. Exclusion Criteria. (The following exclusions are in addition to the general exclusion criteria for the ABSORB IV trial.)

1) Atrial fibrillation.

2) Contraindication to adenosine. Contraindications include including 2nd or 3rd degree heart block; sick sinus syndrome; long QT syndrome; severe hypotension, severe asthma, severe COPD or bronchodilator-dependent COPD.

3) Any condition making it unlikely that the patient will be unable or unwilling to follow all the ischemia substudy procedures.

12.4.2. Test Schedule and Subject Visits

Patients enrolled in the RESOLVE study will not undergo the ABSORB-RESOLVe specific testing in the protocol. Clinical follow-up will continue as per protocol and these patients will remain in full cohort analysis. All related imaging analysis will not be conducted.

12.4.2.1. Baseline CT

- Baseline CT (CT#1) performed after registration/randomization and after PCI but no later than 7 days after implantation of Absorb BVS or XIENCE in all eligible subjects. This test may be performed as an in-patient prior to hospital discharge, or after hospital discharge in a study approved facility.

- For subjects in who the randomized PCI procedure is staged, CT#1 should be performed after the last staged procedure. Other tests, however (SPECT and CT#2) should be performed at a time course based on completion of the first PCI procedure (a similar procedure to clinical follow-up in the main ABSORB IV randomized trial).

12.4.2.2. 14 ± 1 months (i.e. 13-15 months) SPECT

- A 14 ± 1 month SPECT study will be performed for all eligible subjects, except under the following conditions (Figures 12.4.2 a, b):

    - Subjects with stable angina occurring before the 14 ± 1 month SPECT should receive a SPECT exam at the unscheduled visit, if clinically indicated or feasible.

- If SPECT performed at the unscheduled visit shows no evidence of suspected ischemia, the following conditions apply:
  - If the SPECT exam occurred within ≤ 7 months of the index PCI, the 14 ± 1 month SPECT must still be performed.
  - If the SPECT exam occurred > 7 months after the index PCI, the 14 ± 1 month SPECT does not have to be performed; the SPECT performed at unscheduled visit will be analyzed as having met the 14 ± 1 month SPECT requirement.
- If SPECT shows evidence of suspected ischemia at the unscheduled visit, it is strongly recommended that intracoronary angiography (ICA) is performed.
  - If the ICA demonstrates no in-stent restenosis (ISR) and TLR is not performed on <u>all</u> target lesions, the following conditions apply:
    - If the unscheduled visit occurred within ≤ 7 months of the index PCI, the 14 ± 1 month SPECT must still be performed.
    - If the unscheduled visit occurred > 7 months after the index PCI, the 14 ± 1 month SPECT does not have to be performed; the SPECT performed at the unscheduled visit will be analyzed as having met the 14 ± 1 month SPECT requirement.
  - If the ICA demonstrates ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory), the following conditions apply:
    - If TLR is not performed on <u>all</u> target lesions, the 14 ± 1 month SPECT must still be performed.
    - If TLR is performed on <u>all</u> target lesions, or if ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory) <u>in all target lesions</u> is present, the 14 ± 1 month SPECT does not have to be performed; the SPECT performed at the unscheduled visit will be analyzed as having met the 14 ± 1 month SPECT requirement.

- Subjects with severe unstable angina or MI and suspected ISR occurring before the 14 ± 1 month SPECT who can't exercise are not required to undergo SPECT before the unscheduled ICA.
  - If TLR was not performed on <u>all</u> target lesions, a 14 ± 1 month SPECT must still be performed.
  - If TLR is performed on <u>all</u> target lesions, or if ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory) <u>in all target lesions</u> is present, the 14 ± 1 month SPECT does not need to be performed.
- If subjects miss CT#1, they should still undergo the 14 ± 1 month SPECT study.

- All subjects are strongly recommended to discontinue their anti-angina medications (i.e., nitrates, calcium channel blockers, and beta-blockers) 24 hours prior to the SPECT if there are no contraindications to discontinuing. Patients with recurrent angina are not required to discontinue their anti-angina medications.

12.4.2.3. 62 ± 1 month CT

- A 62 ± 1 month CT study will be performed for all eligible subjects, except under the following conditions (Figures 12.4.2.a, c):
    - Subjects with stable angina occurring before the 62 ± 1 month CT study should receive a CT exam at the unscheduled visit, if clinically indicated or feasible. If this event has occurred before 15 months and if SPECT has not yet been performed, this CT may be done on the same day as or within a few days of the SPECT imaging (note: if only one study can be performed in this time period, the SPECT should be given preference). If this event has occurred after 15 months or if SPECT had already been performed, the CT#2 exam should be performed (without SPECT).
    - If the CT performed at the unscheduled visit shows no evidence of suspected ischemia, the following conditions apply:
        - If the CT exam occurred within ≤ 36 months of the index PCI, the 62 ± 1 month CT exam must still be performed.
        - If the CT exam occurred > 36 months after the index PCI, the 62 ± 1 month CT exam does not have to performed; the CT performed at unscheduled visit will be analyzed as having met the 62 ± 1 month CT requirement.
    - If the CT exam shows evidence of suspected ischemia at the unscheduled visit, it is strongly recommended that the subject undergo intracoronary angiography (ICA).
        - If the ICA demonstrates no in-stent restenosis (ISR) and TLR is not performed on <u>all</u> target lesions, the following conditions apply:
            - If the unscheduled visit occurred within ≤ 36 months of the index PCI, the 62 ± 1 month CT exam must still be performed.
            - If the unscheduled visit occurred > 36 months after the index PCI, the 62 ± 1 month CT exam does not have to performed; the CT exam performed at the unscheduled visit will be analyzed as having met the 62 ± 1 month CT requirement.
        - If the ICA demonstrates ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory), the following conditions apply:

- If TLR is not performed on all target lesions, the 62 ± 1 month CT exam must still be performed.

- If TLR is performed on all target lesions, or if ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory) in all target lesions is present, the 62 ± 1 month CT exam does not have to performed; the CT exam performed at the unscheduled visit will be analyzed as having met the 62 ± 1 month CT exam requirement.

- Subjects with severe unstable angina or MI and suspected ISR occurring before the 62 ± 1 month CT exam who can't exercise are not required to undergo the CT exam before the unscheduled ICA.

  - If TLR was not performed on all target lesions, a 62 ± 1 month CT exam must still be performed.

  - If TLR is performed on all target lesions, or if ISR (QCA diameter stenosis > 50% as determined by the angiographic core laboratory) in all target lesions is present, the 62 ± 1 month CT exam does not need to be performed.

- If subjects miss CT#1, they should still undergo the 62 ± 1 month CT exam study.

- All subjects are strongly recommended to discontinue their anti-angina medications (i.e., nitrates, calcium channel blockers, and beta-blockers) 24 hours prior to the CT exam if there are no contraindications to discontinuing. Patients with recurrent angina are not required to discontinue their anti-angina medications.

Both CT and SPECT should be performed in accordance with standard guidelines and standard protocols. The baseline and 62 ± 1 month CT protocol will be performed under rest and pharmacologic stress conditions. The 14 ± 1 month SPECT will be performed under rest and exercise stress conditions. Complete details regarding the each imaging modality and protocol will be provided in the ABSORB-RESOLVe guidance document provided to all participating sites. All participating ABSORB-RESOLVe sites will be required to submit one non-study SPECT and CT study to the core laboratory for site qualification prior to beginning enrollment.

Figure 12.4.2 a. Sub-study design: Overall Trial Flow

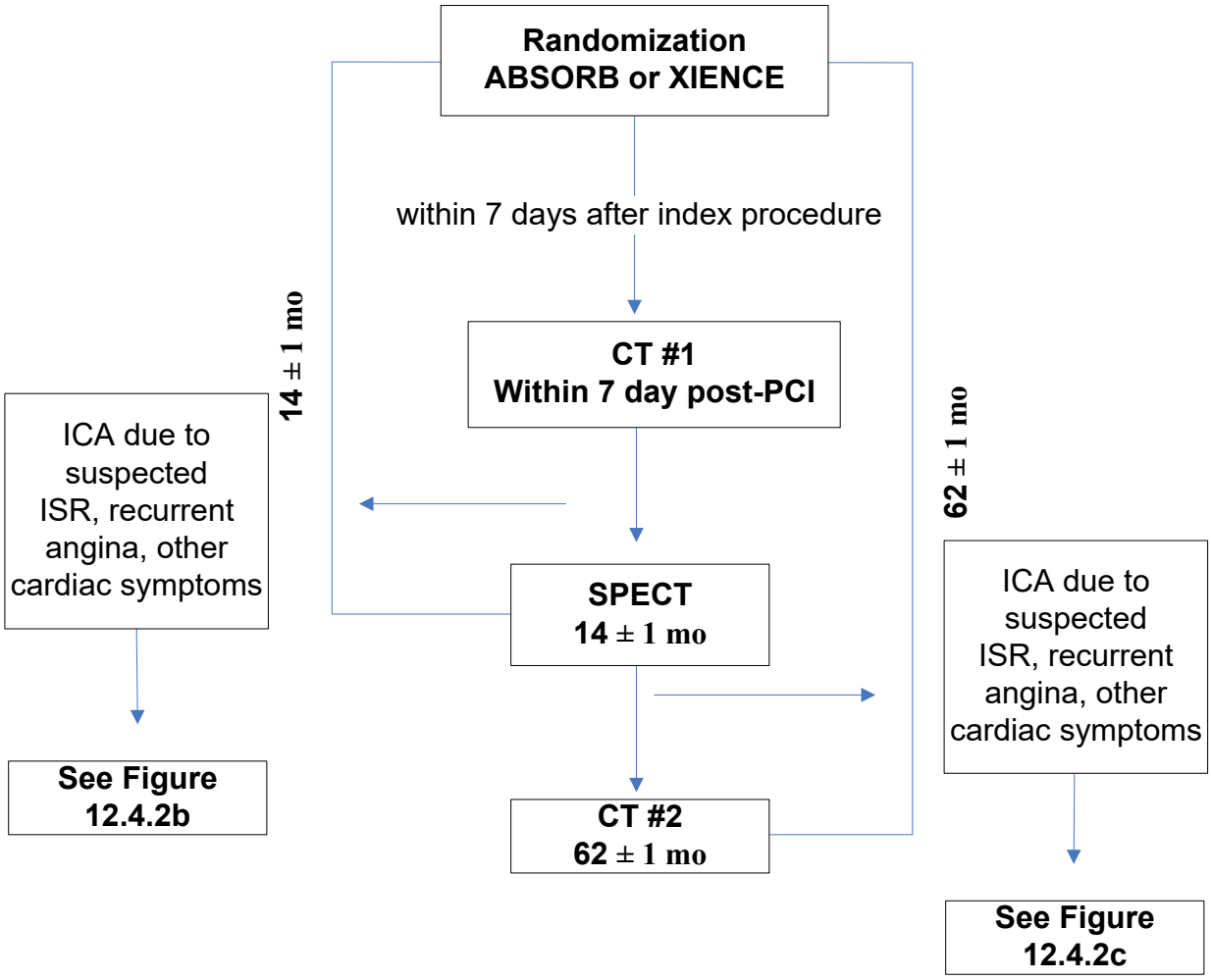


Figure 12.4.2 b. Sub-study design: Unscheduled visit to perform SPECT at < 14 months.

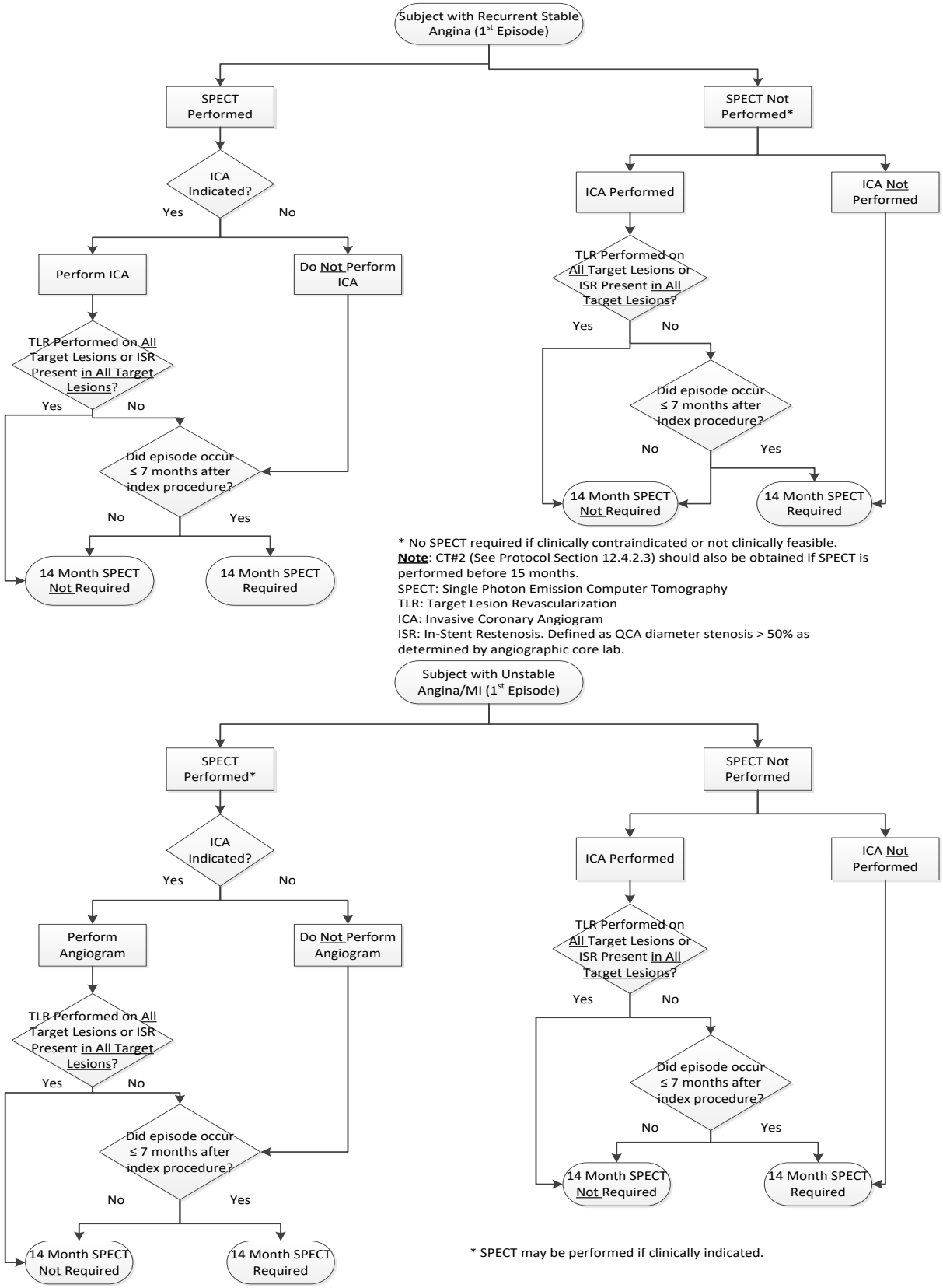
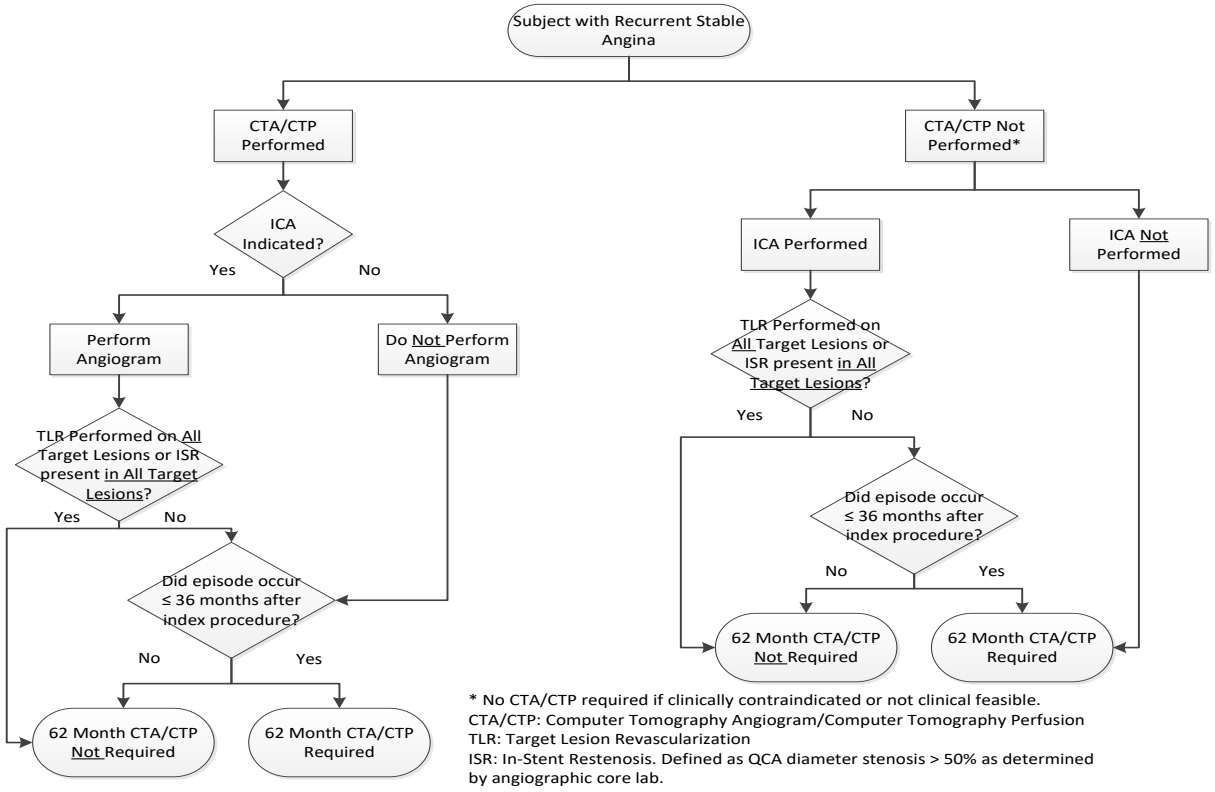
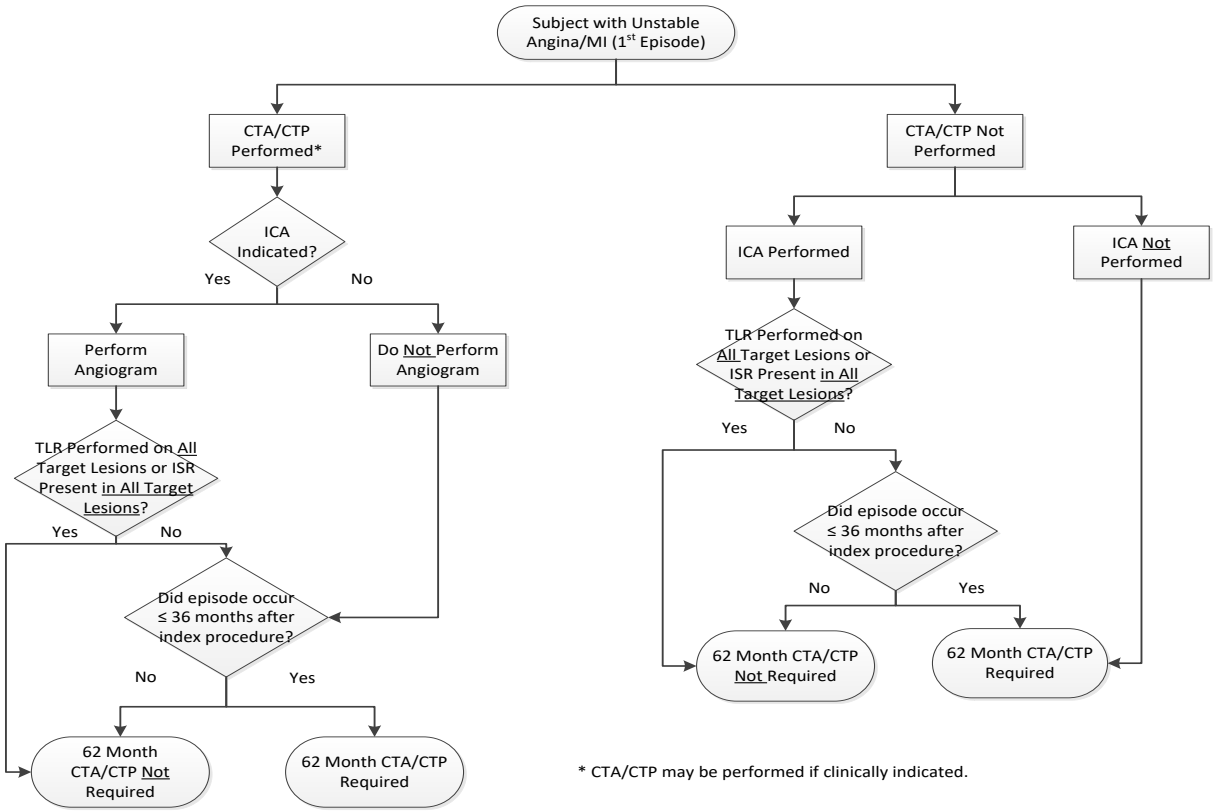


Figure 12.4.2 c. Sub-study design: Unscheduled visit to perform CTA/CTP at < 62 months.





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12.4.3. Procedural Assessments and Treatment Strategy

In the ABSORB-RESOLVe sub-study, all pre-procedure and post-procedure assessments, coronary lesion selection, treatment strategy and antiplatelet regimens must be followed as described in the ABSORB IV parent trial section.

Patients enrolled in the RESOLVE study will not undergo the ABSORB-RESOLVe specific testing in the protocol. Clinical follow-up will continue as per protocol and these patients will remain in full cohort analysis. All related imaging analysis will not be conducted.

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APPENDIX I: ABBREVIATIONS AND ACRONYMS

Please refer to **APPENDIX I** of ABSORB III Protocol (Version 16.0, March 14, 2017) for a complete list of abbreviations and acronyms.

APPENDIX II: DEFINITIONS

Please refer to **Appendix II** of ABSORB III Protocol (Version 16.0, March 14, 2017) for complete list of definitions. New or updated definitions are listed below:

MYOCARDIAL INFARCTION (MI)

Protocol MI Definition: Periprocedural MI definition is modified from Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol. 2013 Oct 22;62(17):1563-70.

This definition will be used for the primary analysis of ABSORB IV and secondary analysis of ABSORB III.

Classification	Biomarker Criteria	Additional Criteria
Periprocedural – patients with a) stable CAD, or b) silent ischemia, or c) acute coronary syndromes with at least 2 baseline troponin values which remained <ULN, or d) acute coronary syndromes in whom the troponin and/or CK-MB levels were elevated but all returned to <ULN prior to the procedure	Absolute CK-MB rises within 48 hours of the procedure to > 5 x ULN for post-PCI or CK-MB > 10 x ULN for post-CABG	Baseline value* < ULN; see also **
Periprocedural – patients with stable CAD and elevated baseline CK-MB, or acute coronary syndromes in whom at least 2 baseline troponin and CK-MB values were drawn and the most recent troponin and CK-MB values were less than the preceding measures by >25%	Absolute incremental CK-MB rise within 48 hours of the procedure from the most recent CK-MB level by > 5 x ULN for post-PCI or > 10 x ULN for post-CABG	
Periprocedural – patients with elevated baseline CK-MB in whom the biomarker levels have not been shown to be stable or falling as defined above (either because only one CK-MB was measured, or the most recent CK-MB measure in a series was either still increasing or had not decreased by	The CK-MB rises within 48 hours of the procedure by an absolute increment from the most recent CK-MB level of > 5 x ULN for post-PCI or > 10 x ULN for post-CABG plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.	The following must also be present: 1. New ST-segment elevation or depression, 2. Plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

>25% from the most recent measure)		
Spontaneous (before or >48 hours after any coronary revascularization procedure)	Troponin >ULN or CK-MB > ULN	One or more of the following must also be present: - Symptoms of ischemia; - ECG changes indicative of new ischemia - (new ST-T changes or new LBBB), - Development of pathological Q waves; - Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality
ULN=Upper limits of the local laboratory normal (will be collected from each hospital laboratory prior to study commencement); LBBB=Left Bundle-branch Block * Baseline CKMB value is required before study procedure and presumes a typical rise and fall post procedure to diagnose a peri procedure MI ** Whenever at least one baseline and one post procedure CK-MB measure are available in a patient with stable CAD, adjudication of MI will be based solely on these biomarker values. If the patient has stable ischemic heart disease and the baseline CK-MB measure are not available, they will be assumed to be within normal limits and MI will be adjudicated by the CEC solely according to the post procedure CK-MB measures. TROPONINS WILL NOT BE USED TO DIAGNOSE PERI-PROCEDURAL MI.		

- **Periprocedural MI After PCI:**

  The periprocedural period includes the first 48 hours after PCI.

- **Periprocedural MI After CABG:**

  The periprocedural period includes the first 48 hours after coronary artery bypass grafting (CABG).

- **Spontaneous MI:**

  MI after the periprocedural period may be secondary to late stent complications or progression of native disease. Performance of ECG and angiography supports adjudication to either a target or non-target vessel in most cases.

  With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short and long-term prognosis, a more sensitive definition than for periprocedural MI of any elevation of troponin or CKMB above the 99th percentile of the upper range limit (or ULN if URL is not available) is used. All late events that are not associated with a revascularization procedure will be considered simply as spontaneous.

Myocardial infarctions will also be adjudicated based on the following classification:

- **Q wave MI**

  Development of new, pathological Q wave on the ECG (≥ 0.04 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads)

- **Non-Q wave MI**

  Those MIs which are not Q-wave MI.

Myocardial infarctions will also be adjudicated as to their relation to the Target Vessel

All infarcts that cannot be clearly attributed to a vessel other than the target vessel will be considered related to the target vessel.

For **Universal** and **WHO MI** definitions, please refer to ABSORB III protocol (Version 17.0, August 16, 2018). These definitions will be used for secondary analysis for ABSORB IV and ABSORB III.

ANGINA

Angina is defined as any angina or angina equivalent symptoms determined by the physician and/or research coordinator after interview of the patient, and as adjudicated by a clinical events committee (CEC).

ADVERSE EVENT [AE]

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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

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

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

Unanticipated serious adverse device effect (USADE) refers to 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.

SERIOUS ADVERSE EVENT [SAE]

If the AE meets any of the criteria below, it is regarded as serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health that either:

1) Resulted in a life-threatening illness or injury, or

2) Resulted in a permanent impairment of a body structure or a body function, or

3) Required in-patient hospitalization or prolongation of existing hospitalization, or

4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

d) An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

DEVICE DEFICIENCY (DD)

Device deficiency (DD) is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

PRODUCT EXPERIENCE (PE)

Product Experience (PE) is defined as any expression of customer concern or dissatisfaction, including adverse events and patient issues that occurred during or after the use of a commercially available medical device.

APPENDIX III: SCHEDULE OF EVENTS

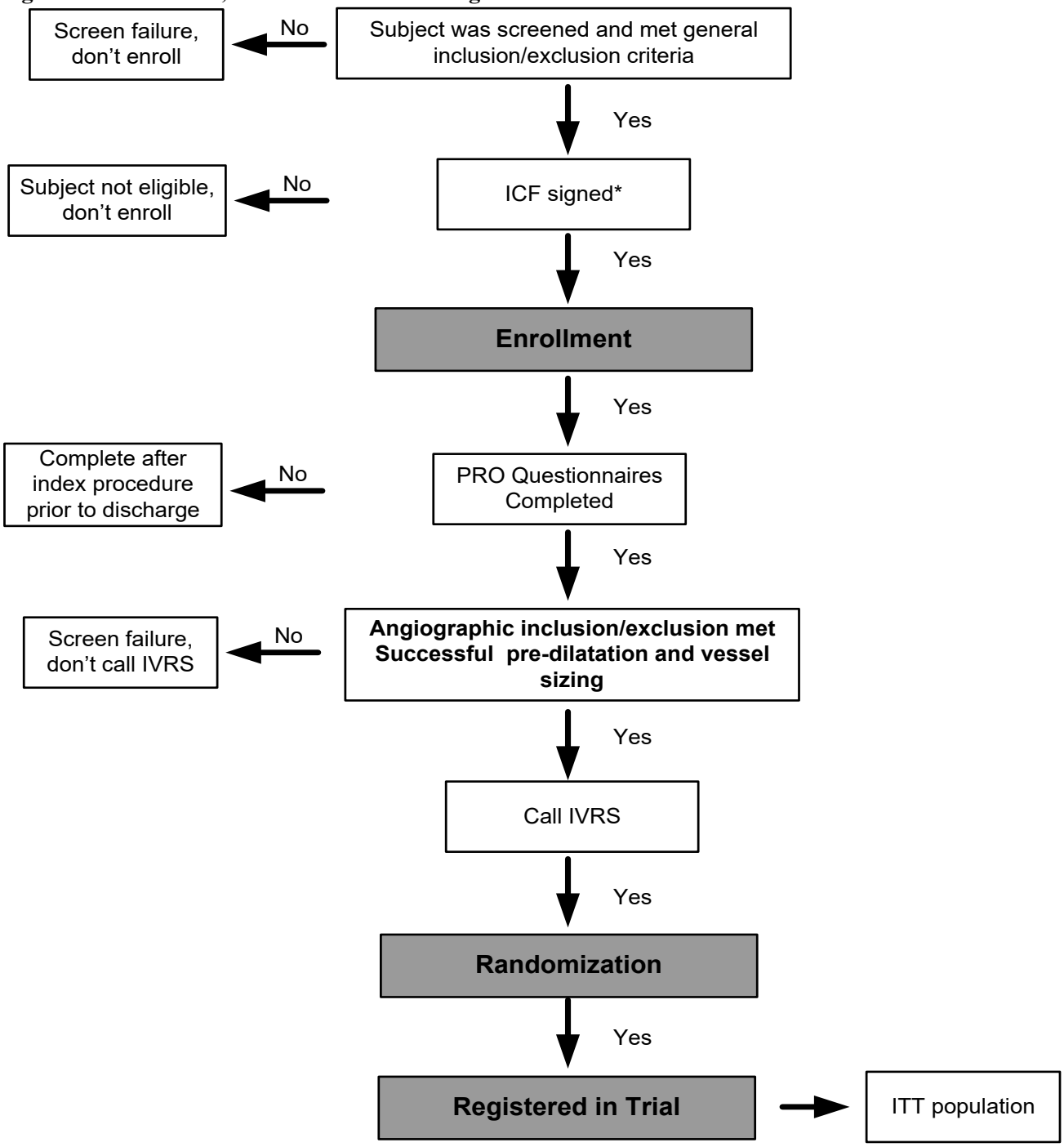
PROCEDURE/TEST	Baseline	Baseline (within 7 days)	Pre-Procedure (within 48 hours)	Procedure	Post-Procedure	30 ±7d, 90 ±14d, 180 ±28d, 270 ± 28d Telephone contact or office visit	14 months ± 1 month	1, 2, 3, 4, 5 yrs (± 28 d), Telephone contact or office visit	62 months ± 1 month	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors, Angina Status, Cardiac History)	✓									
Subject Informed Consent (Must be obtained prior to any study related testing or procedures)	✓									
General Inclusion/Exclusion Criteria[11]	✓									
Angiographic Inclusion/Exclusion Criteria				✓[7]						
Pregnancy Test (if applicable)		✓								
Hgb, Platelet Count, Creatinine, HbA1c, eGFR, WBC	✓[1]									
CK and CK-MB			✓[2]	✓[3]	✓[4]					✓[7]
Troponin I or T			✓[2]	✓[3]						✓[7]
12-lead ECG			✓[5]		✓[5]					✓[7]
Coronary Angiogram				✓[8]						
Study device information				✓						
Per Protocol Medications[6]			✓	✓	✓	✓		✓		✓
Concomitant Medications	✓			✓	✓	✓		✓		✓
Adverse Events				✓	✓	✓		✓		✓
Patient Reported Outcome Instruments	✓[9]					✓[10]		✓[10]		
Patient Perception Questionnaire					✓[12]			✓[12]		
SPECT[14]							✓			✓[15]
CT Angiogram/Perfusion[14]					✓[13]				✓	✓[15]

1. The 21 day lab result must be known prior to index procedure. HbA1c is to be collected in diabetic subjects only, and its result is not needed prior to the index procedure.
2. All patients admitted with the diagnosis of possible acute coronary syndrome (including unstable angina, NSTEMI or STEMI) must have at least one and preferably 2 or more complete sets of biomarkers (a set consisting of troponin (I or T), CK and CK-MB) measured within 24 hours of procedure. Measurements should be at least 6 hours apart if multiple measurements are taken. If the patient has stable coronary artery disease, the pre-procedure CK and CK-MB must be drawn, but can be obtained during the procedure from the arterial sheath but prior to any angioplasty.
3. During the procedure, all patients with ACS (including unstable angina, NSTEMI or STEMI) must have troponin, CK and CK-MB drawn from the arterial sheath prior to first balloon inflation. For patients with stable coronary artery disease, it is strongly recommended to have a CK and CK-MB drawn from the arterial sheath prior to the first balloon inflation.
4. At least two post-procedure draws required: 1) 6 -12 hours post-procedure; 2) 18-24 hours post-procedure or at the time of discharge as long as discharge is at or after 16 hours post-procedure (for hospitals required to discharge stable subjects prior to 16 hours, the subject may be discharged but will have to return to the enrolling institution for their second biomarker draw). If either of the post-procedure CK-MB levels are ≥ 5 x ULN, serial CK and CK-MB levels must be drawn until they are falling.

5. Pre-procedure ECG preferred to be done within 24 hours. Post-procedure ECG must be done within 24 hours post-index procedure.
6. Refer to body of the protocol for details regarding pre-procedure antiplatelet loading requirements. Post-procedure: prasugrel 5 or 10 mg daily, clopidogrel a minimum of 75 mg daily or ticagrelor 90 mg twice daily, must be given for a minimum of 12 months, and Aspirin ≥ 75 mg to ≤ 100 mg daily must be taken through 5 years follow up (potentially up to 10 years follow-up) during the study, and should continue to be taken indefinitely. If a subject develops hypersensitivity to clopidogrel, prasugrel or ticagrelor, subject may be switched to ticlopidine at a dose in accordance with standard hospital practice.
7. For unscheduled visits for suspected ischemic cardiac events, sites should make reasonable efforts to obtain cardiac enzymes (Troponin I or T), CK and CK-MB, and/or ECG if the site is aware of the visit at the time of its occurrence. In all other scenarios (i.e., site does not become aware until after the fact), no protocol deviation will be issued if Troponin I or T, CK and CK-MB, and/or ECG were not obtained at the time of the unscheduled visit.
8. Baseline (prior to pre-dilatation) and final (after stenting/post dilatation) angiogram must be obtained and sent to the core laboratory.
9. Every effort should be made to have subjects complete all patient reported outcomes questionnaires (EQ-5D and SAQ-7) prior to the procedure. However, in situations where this is absolutely not possible, subjects may complete them post-procedure, prior to discharge. Subjects who complete their questionnaires post-procedure should base their responses on their condition prior to the procedure.
10. All registered subjects may complete PRO (EQ-5D and SAQ-7) at 30, 180 days, and at 1, 3 and 5 years.
11. LVEF may be obtained within 6 months prior to the procedure for subjects with stable CAD and for ACS patients it must be assessed within 1 week of the index procedure and after ACS presentation, which may include contrast left ventriculography during the index procedure but prior to randomization in order to confirm the subject's eligibility
12. Administered ≥ 4 hours to ≤ 7 days after the procedure, preferably before hospital discharge, and at 1 year follow-up.
13. Baseline CT Angiogram/Perfusion will be performed up to 7 days after the index procedure or staged procedure, whichever occurs last.
14. Only for subjects in the ABSORB-RESOLVe Ischemia Sub-study. The first CT will be conducted between the day of the index or staged procedure, whichever occurs last, up to 7 days after that procedure. The SPECT will be completed at 14 ± 1 month and the second CT will be conducted at 62 ± 1 month.
15. If a subject enrolled in the ABSORB-RESOLVe Ischemia Sub-study has a cardiovascular related unscheduled event, please follow the procedures outlined in section 12.4.2.2 and 12.4.2.3.

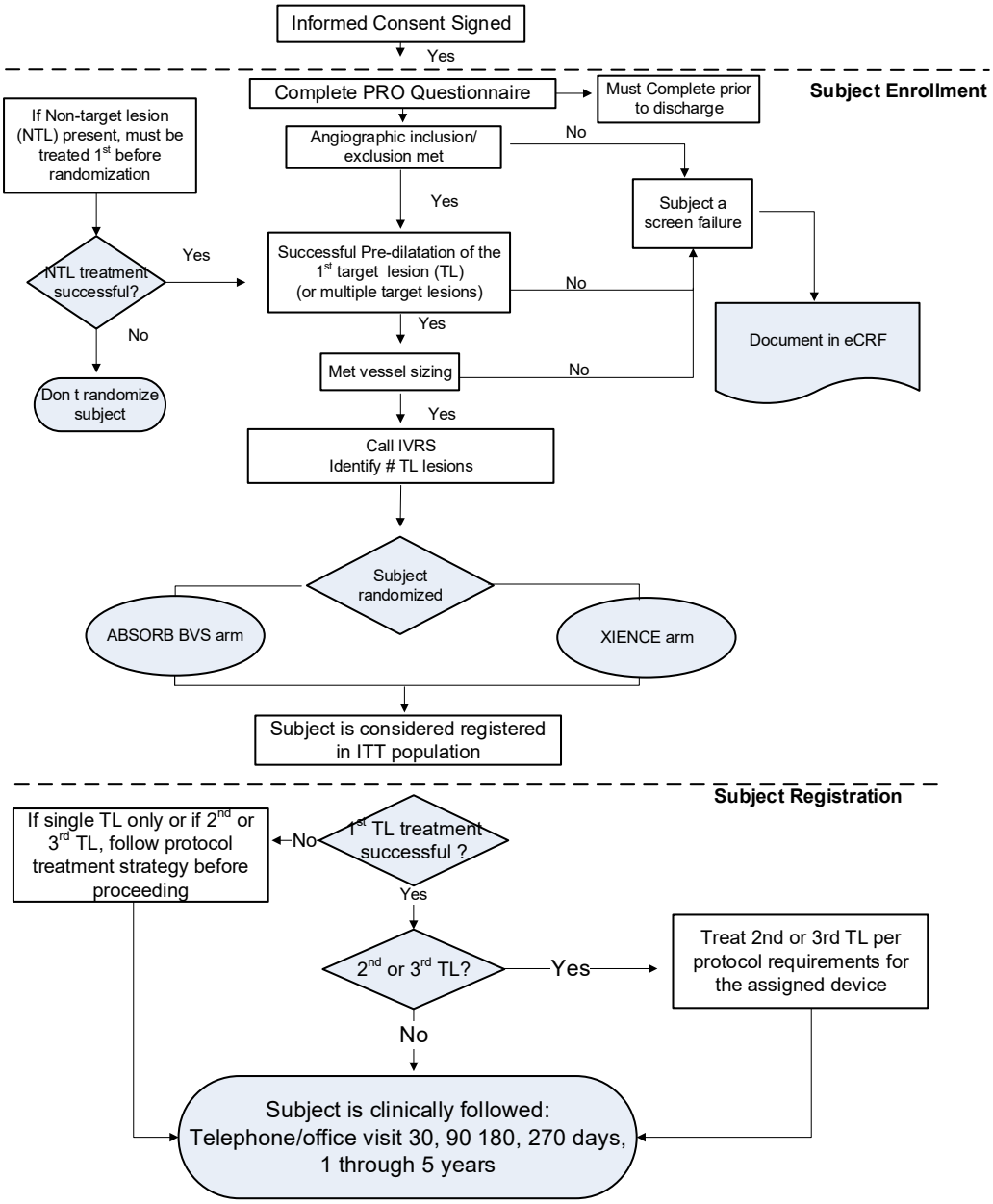
APPENDIX IV: ENROLLMENT AND REGISTRATION PROCESS

Figure 1. Enrollment, Randomization and Registration



* The ICF can be signed before or after the general inclusion criteria screening. Once signed, a subject is considered enrolled.

Figure 2. Enrollment through Treatment Flow

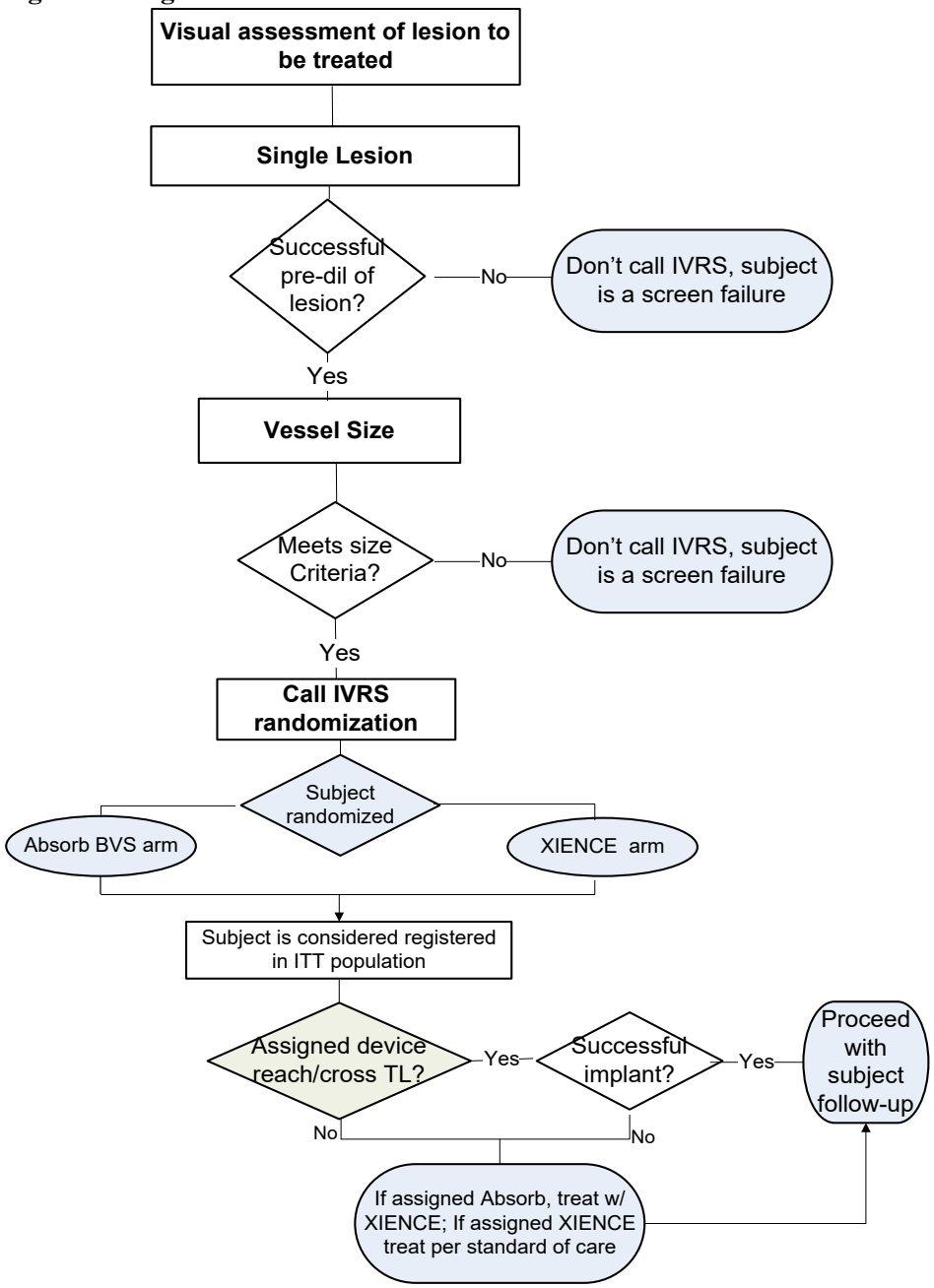


Note:

- The ICF can be signed before or after the general inclusion criteria screening. Once signed, a subject is considered enrolled.
- If there are two or three target lesions, the same vessel sizing modality and treatment requirements must be used on all target lesions.
- Patients in ABSORB IV will potentially be followed up to 5 years if it is necessary as determined by the Sponsor.
- Subjects will be clinically followed up to 5 years
- Patient Reported Outcomes questionnaires should be completed prior to procedure after signing ICF, but must occur prior to discharge. The follow-up PRO questionnaires must be completed at 30 and180 days, and at 1, 3 and 5 years.
- Patient Perception Questionnaire will be administered by the research coordinator post procedure in the hospital prior to discharge (≥ 4 hours to ≤ 7 days after the procedure) and at 1 year.

APPENDIX V: VESSEL TREATMENT & RANDOMIZATION

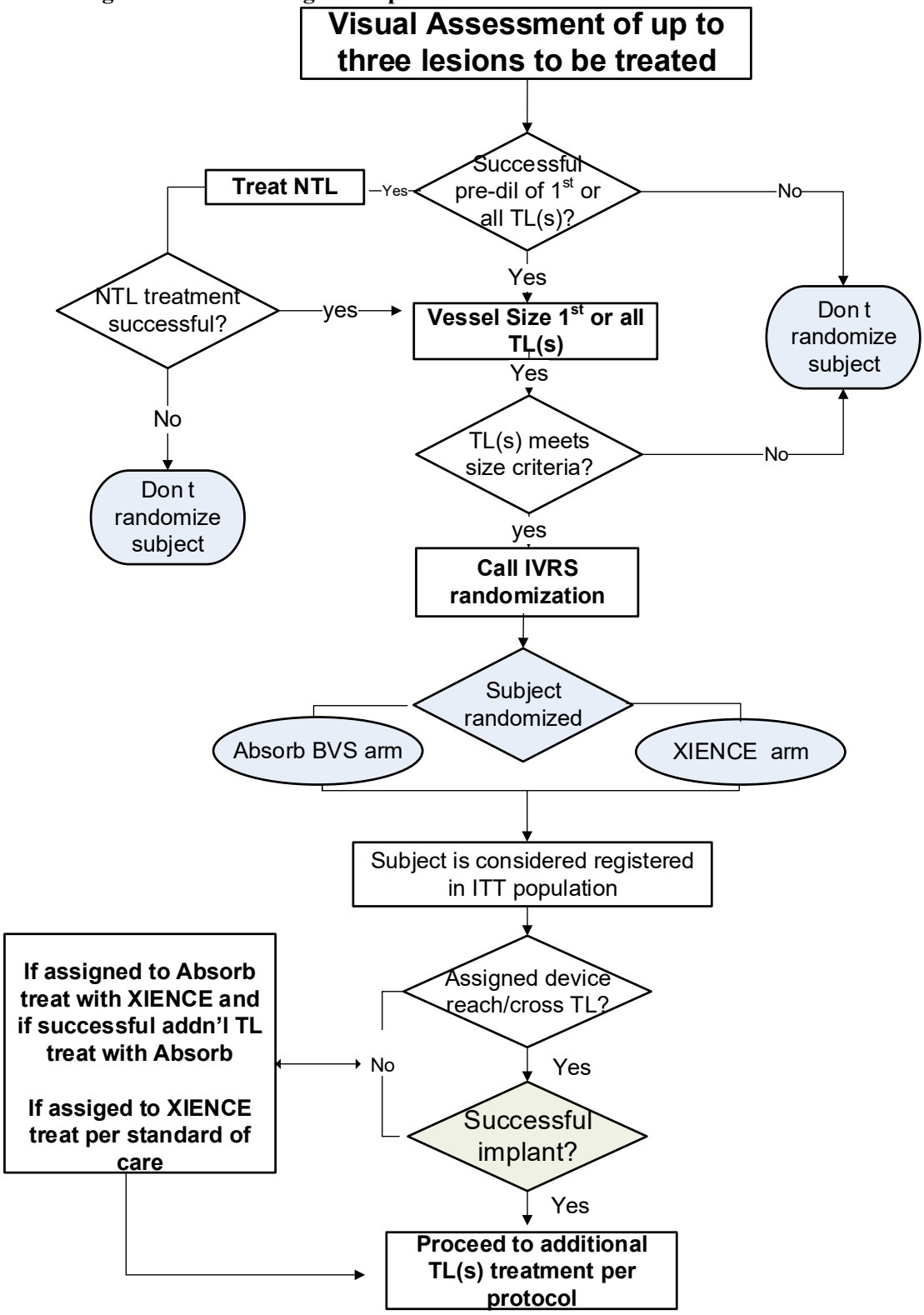
Figure 1. Single Vessel Treatment



Note:

- The lesion must be successfully pre-dilated and meet vessel sizing criteria prior to randomizing subject.
- Due to pre-dilatation being required prior to vessel sizing and randomization, there is the possibility of an "unstable" target lesion. Therefore, time period between pre-dilatation and vessel sizing should be minimized to being as brief as possible.
- Vessel sizing is done by visual estimation.

Figure 2. Vessel Sizing: Multiple Vessel Treatment



Note:

- Non-target lesion treatment can occur only in a non-target vessel. The non-target lesion must be treated first (XIENCE only) prior to randomization. Patient may be randomized only if treatment of the non-target lesion is successful.

- In the case of two or three target lesions, if the 1st target lesion was successfully pre-dilated and eligibility criteria are still met, the operator may at this point choose to randomize the patient, or pre-dilate other lesions. If other lesions are pre-dilated, all such pre-dilatations must be considered successful prior to randomization. If there are two target lesions in a single epicardial coronary artery, it is strongly recommended that both be successful pre-dilated before the patient is randomized.
- If pre-dilatation of the 1st target lesion fails (or if pre-dilatation of any lesion fails if multiple lesions are pre-dilated prior to randomization), the patient may not be randomized.
- If the 1st target lesion was successfully pre-dilated but no longer met eligibility criteria (or if any lesion after pre-dilatation no longer met eligibility criteria if multiple lesions are pre-dilated prior to randomization), the patient may not be randomized.
- In the case of two or three target lesions assigned to the Absorb BVS, if any of the target lesions is unsuccessfully treated with Absorb BVS, XIENCE must be used. If the target lesion that failed treatment of Absorb BVS is treated successfully with XIENCE, the remaining target lesion(s) must be treated with Absorb BVS. If the target lesion failed treatments with both Absorb BVS and XIENCE, all remaining target lesion(s) must be treated per standard of care.
- Due to pre-dilatation being required prior to vessel sizing and randomization, there is the possibility of an "unstable" target lesion. Therefore, time period between pre-dilatation and vessel sizing should be minimized to being as brief as possible.
- Vessel sizing is done by visual estimation.

APPENDIX VI: RISK STRATIFICATION OF CARDIAC CATHERIZATION, STENTING AND PERCUTANEOUS TRANSCATHETER CORONARY ANGIOPLASTY

Potential risks associated with the study device and everolimus were described in the original protocol. Based on additional clinical and commercial experience, and more conservative grouping of MedDRA Preferred Terms, Abbott Vascular can now provide a consolidated list of anticipated adverse events and, in alignment with ISO14155:2011 requirements, the estimated frequencies of those risks.

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures. It is expected that the risks will not be significantly different with the use of the Absorb BVS and XIENCE V stent in this trial. The incidence rates of the known complications that may arise from a stenting procedure were obtained from the pooled XIENCE V trials conducted by AV (Spirit First, Spirit II, Spirit III RCT, Spirit III JPN, Spirit III 4.0 mm, Spirit IV, Spirit V Diabetic, Spirit V Registry, Spirit Women, XV USA, XV DAPT, and XV India using MedDRA Preferred Terms of site-reported 1 year adverse events regardless of relationship to device or procedure) and were classified using the frequency categories as below. Death and stent thrombosis within 1 year have been observed in < 2.0% of the patients enrolled in these trials.

1. Very common: ≥ 10%: Unstable or stable angina pectoris

2. Common: ≥ 1.0% to < 10%: Cardiac, pulmonary or renal failure; access site complications including pain, hematoma, or hemorrhage; vascular complication including at the entry site, which may require vessel repair; coronary artery dissection; arrhythmia including atrial and ventricular; myocardial infarction, including acute myocardial infarction; nausea and vomiting; hypotension; hypertension; restenosis

3. Uncommon: ≥ 0.1% to < 1.0%: Cardiac arrest; emergent or non-emergent surgery; allergic or hypersensitivity reactions to contrast agent or platinum, polymer poly (L-lactide) (PLLA), polymer poly (D,L-lactide) (PDLLA), and drug reactions to everolimus, antiplatelet drugs or contrast agent; bleeding complications which may require transfusion; coronary artery spasm; distal emboli; fever; catheter site infection or pain; myocardial ischemia; palpitations; coronary artery perforation; pericarditis; peripheral ischemia (due to vascular injury); pseudoaneurysm; pulmonary edema; stroke/CVA/TIA; total occlusion of coronary artery; ventricular tachycardia; and ventricular fibrillation; vessel dissection

4. Rare: ≥ 0.01% to < 0.1%: Arteriovenous fistula; cardiac tamponade; coronary artery embolism; arterial injury; procedural nausea; shock; peripheral artery dissection; peripheral nerve injury; renal insufficiency; pericardial effusion

5. Very Rare: < 0.01% (including not reported AEs): Abrupt coronary artery closure; coronary artery aneurysm; arterial rupture; everolimus IFU risks.

Some IFU risks, including everolimus risks have not been observed in AV clinical studies. These risks are listed in the very rare category. There may be risks related to the device that are unknown at present. Likewise the exact frequency of the risk might be unknown.

APPENDIX VII: CONTACT INFORMATION

A list of investigational site co-ordinates can be obtained upon request from the Clinical Project Manager for the study. The Clinical Project Manager can be reached at 408-845-3000.