PROTOCOL #16-308-Redacted
XIENCE 90 Study

Version Number	[redacted]
Date	May 25, 2018
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Trial Type	Prospective, single arm, multi-center, open label trial
Sponsor [redacted]	Abbott Cardiovascular Systems, Inc., A subsidiary of Abbott Vascular, Inc. 3200 Lakeside Drive Santa Clara, CA 95054
[redacted]	[redacted]
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COMPLIANCE STATEMENT:

This trial will be conducted in accordance with this Protocol, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 45 CFR Part 46 and 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.).

PROTOCOL SUMMARY

Trial Name and Number	**XIENCE 90 Study: #16-308-Redacted**
Title	**XIENCE 90 Study**
Trial Device	The commercially approved XIENCE family of coronary drug-eluting stents[1] manufactured by Abbott Vascular, Inc., including: • XIENCE Xpedition (stent diameter 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm, stent length 8, 12, 15, 18, 23 and 28 mm), XIENCE Xpedition SV (stent diameter 2.25 mm, stent length 8, 12, 15, 18, 23, 28 mm) and XIENCE Xpedition LL Everolimus Eluting Coronary Stent System (stent diameter 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm, stent length 33 and 38 mm). • XIENCE Alpine Everolimus Eluting Coronary Stent System: stent diameter 2.25, 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm; stent length 8, 12, 15, 18, 23, 28, 33, and 38 mm. Stent lengths 33 mm and 38 mm are not available for 2.25 mm diameter stent. • XIENCE PRO^{X} Everolimus Eluting Coronary Stent System (OUS only)[2]: stent diameter 2.25, 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm; stent length 8, 12, 15, 18, 23, 28, 33, and 38 mm. Stent lengths 33 mm and 38 mm are not available for 2.25 mm diameter stent. • XIENCE PRO^{A} Everolimus Eluting Coronary Stent System (OUS only)[3]: stent diameter 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm; stent length 8, 12, 15, 18, 23, 28, 33, and 38 mm. Stent lengths 33 mm and 38 mm are not available for 2.25 mm diameter stent. • XIENCE Sierra Everolimus Eluting Coronary Stent System: stent diameter 2.25, 2.5, 2.75, 3.0, 3.25, 3.5 and 4.0 mm; stent length 8, 12, 15, 18, 23, 28, 33, and 38 mm. The above XIENCE family stent system will hereinafter be called "XIENCE" in this study.

[1] The commercially approved XIENCE stent will be used in geographies where it is commercially available
[2] XIENCE PRO^{X} is a rebrand of the XIENCE Xpedition Stent System and is only available outside of the United States.
[3] XIENCE PRO^{A} is a rebrand of the XIENCE Alpine Stent System and is only available outside of the United States.

Objective	The objective of this trial is to evaluate safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk of bleeding (HBR) undergoing percutaneous coronary intervention (PCI) with XIENCE. **Primary Objective:** to show non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT compared to a historical control after propensity score adjustment. **Secondary Objective:** • To show superiority of the major secondary endpoint of major bleeding (Bleeding Academic Research Consortium [BARC] type 2-5) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT compared to a historical control after propensity score adjustment. • To evaluate stent thrombosis (ARC definite/probable) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT against a performance goal (PG).
[redacted]	[redacted]
Clinical Trial Design	A prospective, single arm, multi-center, open label, non-randomized trial to evaluate the safety of 3-month DAPT in HBR subjects undergoing PCI with XIENCE.
Primary Endpoint	The primary endpoint is a composite rate of all death or all myocardial infarction (modified [4]Academic Research Consortium [ARC]) from 3 to 12 months.
Major Secondary Endpoints	• Major bleeding rate (BARC type 2-5) from 3 to 12 months. • Stent thrombosis (ARC definite/probable) from 3 to 12 months
Secondary Endpoints	The following endpoints will be assessed from 3 to 12 months: • All death, cardiac death, vascular death, non-cardiovascular death

[4] Patients present any of the following clinical or imaging evidence of ischemia (symptoms of ischemia; ECG changes indicative of new ischemia - [new ST-T changes or new LBBB], development of pathological Q waves; or imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality), AND confirmed with elevated cardiac biomarkers per ARC criteria (periprocedural MI: CK-MB > 3x URL or Troponin > 3x URL within 48 hours after PCI; CK-MB > 5x URL or Troponin > 5x URL within 72 hours after CABG; Assessment of CK-MB is preferred over troponin for the diagnosis of periprocedural MI, if possible. For spontaneous MI: CK-MB > URL or Troponin > URL) (Circulation 2007; 116: 2344-2351)

	• All myocardial infarction (MI) and MI attributed to target vessel (TV-MI, modified ARC) • Composite of cardiac death or MI (modified ARC) • All stroke, ischemic stroke and hemorrhagic stroke • Clinically-indicated target lesion revascularization (CI-TLR) • Clinically-indicated target vessel revascularization (CI-TVR) • Target lesion failure (TLF, composite of cardiac death, TV-MI and CI-TLR) • Target vessel failure (TVF, composite of cardiac death, TV-MI and CI-TVR) • Major bleeding defined by the Bleeding Academic Research Consortium (BARC) type 3-5
Point of Registration	Subject registration will occur after the index procedure but prior to discharge and up to 3 days post index procedure, upon confirmation of the following: • Signed informed consent has been obtained; • Subject has met all the inclusion and none of the exclusion criteria (including both general and angiographic criteria). Planned staged procedures are allowed (recommend to be performed within 30 days). The site may consent the subject after the initial procedure. Subject registration will occur once the last staged procedure is performed and the last staged procedure is considered as the index procedure.
Subject Follow-Up	Subjects registered in the trial will receive the following clinical follow-up: • 3 months (90 ± 7 days): office visit (Note: A formal office visit is required at 3-month follow-up to ensure a thorough clinical evaluation. A telephone contact is an option only for subjects who would otherwise be lost to follow-up due to being unable to complete an office visit, but a formal follow-up visit is still preferred at 3 months.) • 6 months (180 ± 14 days): office visit/ telephone contact (office visit is strongly recommended whenever possible) • 12 months (365 ± 28 days): office visit/ telephone contact (office visit is strongly recommended whenever possible)
Primary Analysis Sample Size Justification	To evaluate the safety of the 3-month DAPT, non-inferiority (NI) will be tested comparing 3-month DAPT to XIENCE V USA historical control for the primary endpoint of all death or all myocardial infarction (modified ARC) from 3- to 12-month follow-up in a "3-month clear" population (defined as subjects who are free

	from myocardial infarction [modified ARC], repeat coronary revascularization, stroke, or stent thrombosis [ARC definite/probable] within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days). [redacted] • [redacted]
Major Secondary Analysis	Given the success of the primary analysis for the primary endpoint, the following major secondary analyses will be performed: • Superiority test for major bleeding rate (BARC type 2-5) from 3- to 12-month follow-up will be tested between XIENCE 90 and the XIENCE V USA historical control stratified by propensity scores. • Stent thrombosis (ARC definite/probable) from 3- to 12-month follow-up of XIENCE 90 will be evaluated against a pre-specified PG. Details of the above major secondary analyses could be found in the Statistical Analysis Plan (SAP).
Antiplatelet Medication	**Antiplatelet Medication Loading Dose:** • Subjects must receive a loading dose of aspirin AND a P2Y12 inhibitor (Clopidogrel, Prasugrel or Ticagrelor). The dosages of aspirin and P2Y12 inhibitor shall be determined by physician per standard of care and label indication for loading dose usage. The choice of P2Y12 inhibitor is per site standard of care, but clopidogrel is strongly recommended for HBR subjects. Per physician's discretion, a loading dose of P2Y12 inhibitor may be omitted if the subject was on chronic usage for ≥ 7 days.

Antiplatelet Medication Post-Procedure Daily Dose:

- All subjects must receive ≥75 to ≤100 mg of aspirin daily throughout the study. All subjects must maintain a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most subjects*) or 90 mg twice daily of ticagrelor for at least 3 months following the procedure.
  - The choice of P2Y12 inhibitor is per site standard of care, but clopidogrel is strongly recommended for HBR subjects.
  - For subjects taking chronic anticoagulants, dual therapy (oral anticoagulant and a P2Y12 inhibitor, clopidogrel preferred) may be considered for the first 3 months after index procedure per investigator's discretion.
- At 3-month follow up, subject will be assessed for their eligibility of P2Y12 inhibitor discontinuation. Eligible subjects will discontinue P2Y12 inhibitor and receive ≥75 to ≤100 mg of aspirin daily through 1-year follow-up during the study if they are "3-month clear", defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

  [redacted]
- Subjects who are not "3-month clear" are NOT eligible for P2Y12 inhibitor discontinuation at 3-month. These subjects will be treated per the investigator's discretion and will continue to be followed up through 12 months.

*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.

Cardiac Biomarker Collection	Cardiac biomarker CK, CK-MB and/or troponin collection shall be done per site's standard of care. CK and CK-MB are preferred. If CK and CK-MB are not available, troponin should be collected.
Key Inclusion Criteria	**General Inclusion Criteria** 1. Subject is considered at high risk for bleeding (HBR), defined as meeting one or more of the following criteria at the time of registration and in the opinion of the referring physician, the risk of major bleeding with > 3-month DAPT outweighs the benefit: a) ≥ 75 years of age. b) Clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy. c) History of major bleeding which required medical attention within 12 months of the index procedure. d) History of stroke (ischemic or hemorrhagic). e) Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent). f) Systemic conditions associated with an increased bleeding risk (e.g. hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk). g) Anemia with hemoglobin < 11g/dl. 2. Subject must be at least 18 years of age. 3. Subject or a legally authorized representative must provide written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site prior to any study related procedure. 4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at 3 months, if eligible per protocol. 5. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure. **Angiographic Inclusion Criteria** 1. Up to three target lesions with a maximum of two target lesions per epicardial vessel. Note: • The definition of epicardial vessels means left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX) and right coronary artery (RCA) and their branches. For example, the patient must not have >2 lesions

	requiring treatment within both the LAD and a diagonal branch in total. • 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. 2. Target lesion ≤ 32 mm in length by visual estimation. 3. Target lesion must be located in a native coronary artery with visually estimated reference vessel diameter between 2.25 mm and 4.25 mm. 4. Exclusive use of XIENCE family of stent systems during the index procedure. 5. Target lesion has been treated successfully, which is defined as achievement of a final in-stent residual diameter stenosis of <20% with final TIMI-3 flow assessed by online quantitative angiography or visual estimation, 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 > 0.5 mm or depression lasting > 5 minutes.
Key Exclusion Criteria	**General Exclusion Criteria** 1. Subject with an indication for the index procedure of acute ST-segment elevation MI (STEMI). 2. Subject has a known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, P2Y12 inhibitors (clopidogrel/prasugrel/ticagrelor), everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated. 3. Subject with implantation of another drug-eluting stent (other than XIENCE) within 9 months prior to index procedure. 4. Subject has a known left ventricular ejection fraction (LVEF) <30%. 5. Subject judged by physician as inappropriate for discontinuation from P2Y12 inhibitor use at 3 months, due to another condition requiring chronic P2Y12 inhibitor use. 6. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 3 months following index procedure. 7. Subject with a current medical condition with a life expectancy of less than 12 months.

	8. Subject intends to participate in an investigational drug or device trial within 12 months following the index procedure. 9. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test. **Note**: Female patients of childbearing potential should be instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches, hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilised regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the study design, product characteristics and/or study population 10. Subject is part of a vulnerable population, 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. 11. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint. **Angiographic Exclusion Criteria** 1. Target lesion is in a left main location. 2. Target lesion is located within an arterial or saphenous vein graft. 3. Target lesion is restenotic from a previous stent implantation. 4. Target lesion is a total occluded lesion (TIMI flow 0).

	5. Target lesion contains thrombus as indicated in the angiographic images (per SYNTAX score thrombus definition). 6. Target lesion is implanted with overlapping stents, whether planned or for bailout. Note: If there is more than one target lesion, all target lesions must satisfy the angiographic eligibility criteria. Non-target lesion (i.e., lesions that do not meet the angiographic criteria listed above) treatments are not allowed during the index procedure.
Primary Analysis Population	The primary analysis population is "3-month clear" population, defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

1.0 INTRODUCTION

1.1 Trial Design

XIENCE 90 study is a prospective, single arm, multi-center, open label trial to evaluate the safety of 3-month dual antiplatelet therapy (DAPT) in subjects at high risk of bleeding (HBR) undergoing percutaneous coronary intervention (PCI) with the approved XIENCE family of coronary drug-eluting stents.

The XIENCE family stent systems include commercially approved[5] XIENCE Xpedition Everolimus Eluting Coronary Stent System (EECSS), XIENCE Alpine EECSS, XIENCE PRO^{X} EECSS (OUS only)[6], XIENCE PRO^{A} EECSS (OUS only)[7], and XIENCE Sierra EECSS, which are all manufactured by Abbott Vascular, Inc., Santa Clara, USA. The above XIENCE family stent systems will hereinafter be called "XIENCE" in this study.

[redacted] Study population consists of non-complex HBR subjects with up to three native coronary artery lesions (a maximum of two lesions per epicardial vessel) with reference vessel diameter between 2.25 mm and 4.25 mm. Eligibility of P2Y12 receptor inhibitor discontinuation will be assessed at 3-month follow-up. Subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days are considered as "3-month clear", and will discontinue P2Y12 receptor inhibitor and continued with aspirin monotherapy after 3-month follow-up.

All registered subjects will be followed at 3, 6 and 12 months post index procedure.

The data collected from the XIENCE 90 study will be compared with the historical control of non-complex HBR subjects treated with standard DAPT duration of up to 12 months from the XIENCE V USA study, which is a US post-approval study to evaluate the safety of XIENCE V EECSS in "all-comer" population under real-world setting.

1.2 Trial Objective

Primary Objective: to show non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT compared to a historical control after propensity score adjustment.

Secondary Objective:

- To show superiority of the major secondary endpoint of major bleeding (Bleeding Academic Research Consortium [BARC] type 2-5) from 3 to 12 months following

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[6] XIENCE PRO^{X} is a rebrand of the XIENCE Xpedition Stent System and is only available outside of the United States.
[7] XIENCE PRO^{A} is a rebrand of the XIENCE Alpine Stent System and is only available outside of the United States.

XIENCE implantation in HBR subjects treated with 3-month DAPT compared to a historical control after propensity score adjustment.

- To evaluate stent thrombosis (ARC definite/probable) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT against a performance goal (PG).

2.0 BACKGROUND INFORMATION

2.1 Background and Rationale

Although drug-eluting stents (DES) have been shown to effectively reduce restenosis compared with bare-metal stents (BMS), there was a concern that DES might lead to an increased risk of stent thrombosis based on data from first-generation DES[1-4]. This increased risk has been attributed, in part, to polymer hypersensitivity reactions, delayed arterial healing, endothelial dysfunction, and late acquired stent malapposition. Stent thrombosis generally will manifest in serious clinical outcomes of MI and/or death. As a result of this concern, the previous 2011 ACCF/AHA/SCAI guidelines recommend a prolonged duration of DAPT, a continuation of at least 1 year of DAPT following DES implantation as compared to a minimum of 1 month of DAPT following BMS implantation for patients without acute coronary syndrome (ACS)[5]. However, these recommendations were based primarily on observational data with the first generation DES. Compared with first-generation DES, currently used second-generation DES have a lower risk of stent thrombosis. Data from five RCTs [6-10]of primarily low-risk patients (non-ACS) treated with DES comparing shorter-duration (3 to 6 months) DAPT with 12 months of DAPT, as well as several meta-analyses and data review[11-16], did not find an increased risk of stent thrombosis with shorter duration of DAPT. Therefore, the most recently published 2016 ACC/AHA guideline updated their recommendations to decrease the minimum DAPT duration from 12 months to 6 months after DES implantation in patients with stable ischemic heart disease (SIHD)[17].

Long-term DAPT is known to increase the risk of bleeding. Multiple studies have demonstrated the relationship between bleeding and an increased risk for short- and long-term mortality[18,19], with major bleeding being identified as an independent predictor of mortality with a weight similar to or event greater than MI[20]. This was confirmed in a recent meta-analysis by Palmerini with 12 trials comprising > 34,000 patients randomized to different duration strategies of DAPT[21]. In this meta-analysis (including patient level data of 11,473 patients from 6 of those 12 RCT trials), bleeding was an independent predictor of mortality occurring within 1 year of the bleeding episode (hazard ratio: 6.93; 95% CI: 4.53 to 10.60; $p < 0.0001$). More importantly, shorter DAPT was associated with lower rates of all-cause mortality compared with longer DAPT, which was driven by lower rates of bleeding-related deaths with shorter DAPT duration. This important finding may underlie the potential mortality benefit with shorter DAPT, which is especially relevant for patients who are at high risk of bleeding (HBR).

HBR patients represent approximately 15% or more of patients undergoing PCI[22,23]. This patient population is of a significant size but is usually excluded from traditional DES approval trials. The traditional standard treatment for HBR patients who undergo percutaneous coronary intervention (PCI) is often stenting with BMS followed by 1 month of DAPT. While this strategy aims to minimize the risk of bleeding in such patients, the use of BMS poses a higher risk of restenosis and re-intervention. Therefore, stenting with DES followed by a shortened course of DAPT may represent a more favourable treatment option providing that the potential risk of stent thrombosis can be addressed. With advances in stent technology, second-generation DES is equipped with novel stent materials and designs,

polymers, and anti-proliferative agents, which may modify the propensity of DES for ischemic events. It is possible that the same level of safety may be maintained for second-generation DES even if combined with a significantly shortened course of DAPT. In fact, the European ESC/EACTS guidelines have recommended 3 months of DAPT with second-generation DES for HBR patients undergoing PCI[24]. Consistent with the European guideline, the updated 2016 ACC/AHA guideline also provided a class IIb recommendation of 3-month DAPT in SIHD patients with high risk of bleeding following DES implantation[17].

The second generation everolimus-eluting stent (EES) has been the subject of extensive clinical studies across multiple geographies. A consistently low late and very late stent thrombosis rate has been demonstrated with EES from randomized controlled studies [25-30] as well as real-world registry studies [31,32]. The XIENCE family of stents has consistently been shown to have the best safety profile among coronary stents, including second-generation DES.

To investigate whether there are any major differences in the risk of stent thrombosis between first- and second-generation DES, or between DES and BMS, Palmerini et al. conducted a comprehensive network meta-analysis involving 50,844 patients from 49 RCTs implanted with DES or BMS[33]. This meta-analysis demonstrated that XIENCE V had the lowest rate of stent thrombosis within 2 years of implantation compared with other stents. Not only was XIENCE V associated with significantly lower 1-year rate of definite stent thrombosis than the other first- and second-generation DES, including Cypher, Taxus, Endeavor, and Resolute, XIENCE V was also associated with significantly lower rates of definite stent thrombosis than BMS at both 1 year (odds ratio [OR]: 0.23, 95% confidence interval [CI]: 0.13-0.41) and 2 years (OR: 0.35, 95% CI: 0.17-0 .69), a result not duplicated by other DES. The reduction in stent thrombosis with XIENCE V compared with BMS was apparent both early (0-30 days) and late (31 days-1 year), suggesting the reduction was not caused by the difference in DAPT durations between XIENCE V and BMS as the reduction was already evident as early as 30 days when all patients should be treated with DAPT regardless of device types.

Another recent large meta-analysis involving 106,427 patients from 126 RCTs was conducted to compare the safety and efficacy of these biodegradable polymer DES (BP-DES) with those of durable polymer DES and BMS[34]. Among all the stents compared, XIENCE V was the safest with a lower risk of clinical events when compared to DES, including BP-DES and other first and second generation DES. Even when compared to BMS, XIENCE V was still associated with significant reductions in the rates of definite stent thrombosis (rate ratio: 0.35, 95% CI: 0.21 to 0.53), MI (rate ratio: 0.65, 95% CI: 0.55 to 0.75), and death (rate ratio: 0.72, 95% CI: 0.58 to 0.90).

Even in the setting of elevated risk for thrombosis such as acute coronary syndrome, XIENCE V still demonstrated a favourable safety outcome as reported in the EXAMINATION trial, which was an all-comer trial randomizing 1,504 subjects with ST-segment elevation myocardial infarction (STEMI) in a 1: 1 ratio to XIENCE V or BMS (Vision). This study demonstrated that XIENCE V was associated with reduced rates of stent thrombosis compared with BMS at 1 year and 2 years, with the rates becoming comparable between the two groups at 3, 4, and 5 years with similar DAPT usage at 5-year follow-up [35,36]. It suggests that the risk of stent thrombosis with XIENCE V, if not lower, is at least comparable to that of BMS even in this high risk STEMI population.

The excellent safety profile of XIENCE in terms of stent thrombosis is likely attributed to the unique combination of its thin struts (81 μm), the thromboresistant nature of the biocompatible fluoropolymer[37], and a low loading dose and release kinetics of the anti-

proliferative agent, everolimus. Autopsy studies in humans have suggested that incomplete endothelialization of strut surface is a pathologic substrate for late stent thrombosis[38,39]. In a pre-clinical study conducted in rabbit iliac arteries, areas between struts showed most complete coverage (90.4%) for EES compared with other stents at 14 days[40]. The rapid strut coverage by endothelium with XIENCE V was confirmed in humans in an optical coherence tomography (OCT) cohort of the MECHANISM-Elective study[41], which showed 93.6% strut coverage at 1 month (N=49) and 98% strut coverage at 3 months (N=46) in subjects with stable coronary artery disease receiving XIENCE V.

The XIENCE family of stents is unique from other currently marketed stents in featuring a fluorinated co-polymer coating [poly (vinylidene fluoride-co-hexafluoropropylene)] (PVDF-HFP). This polymer coating not only serves as the vehicle for the controlled elution of everolimus, but just as importantly the fluorinated co-polymer offers a non-thrombogenic surface through a mechanism known as fluoropassivation[42]. Pre-clinical models comparing inflammation and platelet adhesion among XIENCE V, BMS and Resolute showed that XIENCE V had a lower propensity for inflammation and platelet adhesion[43,44]. In a series of *ex vivo* studies using porcine arterio-venous shunt model to assess and compare the thrombogenicity of XIENCE to different stent platforms, XIENCE showed a significant reduction in acute thrombus formation (measured as platelet adhesion) in comparison to BMS as well as new generation of bioresorbable polymer-coated stent (Synergy) and polymer-free stent (BioFreedom)[8]. The high degree of stent coverage within 1 and 3 months of implant, together with the results of *ex vivo* studies which consistently showed low thrombogenic potential of XIENCE through the unique properties of its fluorinated co-polymer coating, provides further evidence to support the safety of shorter DAPT with XIENCE.

Short-term DAPT has been recently studied in HBR patients. The ZEUS study is a randomized, single-blind trial evaluating Endeavor DES vs. BMS combined with a tailored course of DAPT for treating subjects who were considered uncertain DES candidates, including HBR patients, patients at high risk for thrombosis, and patients at low risk for restenosis[45]. A total of 1,606 subjects were randomized in a 1:1 ratio to either Endeavor or thin-strut BMS (strut thickness < 100 μm). DAPT duration was prescribed based on patient characteristics, rather than stent characteristics, and a personalized regimen of 1-month DAPT was allowed. The primary endpoint of the study was MACE (death, MI, or target vessel revascularization [TVR]) at 1 year. In this study, approximately half of the enrolled subjects were HBR patients (51.6%), who were qualified for 1-month DAPT. In the pre-specified HBR subgroup analysis from ZEUS trial, MACE occurred in 22.6% of the Endeavor group and 29% of the BMS group with a hazard ratio 0.75 (p=0.033)[46]. The definite or probable ST was also significantly reduced in the Endeavor group (2.6% vs. 6.2%, p=0.016).

The LEADERS FREE study is a randomized, double-blind trial evaluating BioFreedom combined with 1 month of DAPT for treating HBR patients undergoing PCI as compared to BMS[47]. A total of 2,466 HBR patients were randomized in a 1:1 ratio to BioFreedom or a very similar BMS (Gazelle). All patients received 1 month of DAPT and were to be followed at 1, 2, and 4 months, and 1 and 2 years. The primary safety endpoint, tested for both non-inferiority and superiority, was a composite of cardiac death, MI, or stent thrombosis

[8] Data on file with Abbott Vascular

(definite/probable). The primary efficacy endpoint was clinically driven target lesion revascularization (CD-TLR). At 1 year, the rate of the composite of cardiac death, MI, or stent thrombosis was significantly lowered in the BioFreedom group than in the BMS group (9.4% (112/1221) vs. 12.9% (154/1211); P < 0.001 for noninferiority and P=0.005 for superiority). The 1-year rate of CD-TLR was also significantly lower in the BioFreedom group than in the BMS group (5.1% (59/1221) vs. 9.8% (113/1211), P <0.001). There was also a significant reduction in the 1-year rate of MI with BioFreedom compared with BMS (6.1% vs. 8.9%, p = 0.01), whereas no differences in the 1-year rates of stent thrombosis were observed between the two groups (2.0% vs. 2.2%, p = 0.75).

Results from both ZEUS and LEADER FREE suggest that DES can be as safe or even safer choice for HBR patients than BMS with short duration of DAPT. The confirmed safety of Endeavor and BioFreedom with short-term DAPT for HBR patients in the ZEUS and LEADERS FREE studies are of particular relevance to the safety of the proposed study of XIENCE. XIENCE V has consistently been shown to have a better safety profile than Endeavor based on results from several meta-analyses[33,34]. Pre-clinical studies of endothelialization also demonstrate that XIENCE V had a faster rate of strut coverage following stent implantation than Endeavor [40], and was equivalent to BioFreedom[48]. Additionally, XIENCE showed a significant reduction in platelet adherence compared to BioFreedom stents in *ex vivo* studies[9]. Taken together, these clinical data of Endeavor and BioFreedom indirectly support the safety to evaluate short-term DAPT with XIENCE.

There is also clinical data exclusively evaluating short DAPT duration with XIENCE. STOPDAPT trial is a prospective multi-center, single-arm study evaluating 3-month DAPT duration after XIENCE implantation in 1,525 patients[49] . Using the XIENCE group in the RESET trial as a historical comparison group, where nearly 90% of patients were on DAPT at 1 year, the cumulative incidence of the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke, definite stent thrombosis and TIMI major/minor bleeding) at 1 year tended to be lower in the STOPDAPT than in the RESET (2.8% vs. 4.0%, p = 0.06). The difference is driven by the significantly lower rate of the composite major secondary endpoint of cardiovascular death, myocardial infarction, stroke and definite stent thrombosis rate (2.1% vs. 3.2%, p = 0.045) while the TIMI major/minor bleeding rates were similar between the two groups (1.0% vs. 1.3%, p = 0.4). The cumulative incidence of definite/probable stent thrombosis was also lower in the STOPDAPT (0% vs. 0.3%, p = 0.03). The STOPDAPT trial data support the safety of short-term DAPT following XIENCE V implantation.

To assess the relationship between stent thrombosis and DAPT usage, a patient-level pooled analysis was conducted on a total of 11,219 patients who had complete DAPT usage data through the 2-year follow-up period from seven Abbott Vascular-sponsored XIENCE V trials (including three pre-approval trials: SPIRIT II, III, IV, and four post-approval single-arm registry studies: XIENCE V USA, XIENCE V India, SPIRIT V and SPIRIT Women)[50] . DAPT requirement varied among these studies. For the three randomized pre-approval trials, at least 6 months of DAPT was required in the protocol. In the four single-arm registry studies, DAPT usage was recommended as per standard of care. The large sample size in this pooled analysis allows for a more robust evaluation of stent thrombosis and its association

[9] Data on file with Abbott Vascular

with DAPT interruption/discontinuation for patients implanted with XIENCE V. In this pooled analysis, the overall rate of definite/probable stent thrombosis at 2 years was 0.75%, with 0.36% for early stent thrombosis (within 1 month), 0.29% for late stent thrombosis (1-12 months) and 0.11% for very late stent thrombosis (after 1 year). The risk of stent thrombosis with permanent DAPT discontinuation after 3 months was low, with similar ST rate through 2 years compared to those without permanent DAPT discontinuation (0.78% vs. 0.83%, respectively). By propensity and DAPT usage adjusted multivariable analysis, permanent DAPT discontinuation in any interval after 90 days was not associated with the occurrence of ST.

The optimal duration of DAPT remains a dilemma for clinicians with the current clinical practice. The possible benefits of extended DAPT therapy to prevent late stent thrombosis and the progression of atherosclerotic disease need to be weighed against the increased risk of bleeding in an individual patient based on stent type. The optimal duration of DAPT is of particular interest to HBR patients, in whom it is believed that the benefit of reduced bleeding with shorter DAPT outweighs the potential risk of thrombosis and ischemic events. There is clearly an unmet medical need to be addressed for this patient population. XIENCE has consistently been shown to have the best safety profile among the coronary stents, even when compared to BMS and biodegradable polymer DES. The benefit/risk ratio of a shorter duration of DAPT following XIENCE implantation in this population has not been thoroughly evaluated. Therefore, the XIENCE 90 study is designed to prospectively evaluate the safety of XIENCE followed with 3-month DAPT in HBR patients.

2.2 Summary of Investigational Device

2.2.1 Name of the Investigational Device

- XIENCE Xpedition®, XIENCE Xpedition® Small Vessel (SV) and XIENCE Xpedition® LL Everolimus Eluting Coronary Stent System (XIENCE Xpedition Stent System; P110019 / S025, approved on December 21, 2012)
- XIENCE Alpine® Everolimus Eluting Coronary Stent System (XIENCE Alpine Stent System; P110019 / S070; approved on September 3, 2014)
- XIENCE PRO^{X} Everolimus Eluting Coronary Stent System[10]
- XIENCE PRO^{A} Everolimus Eluting Coronary Stent System[11]
- XIENCE Sierra Everolimus Eluting Coronary Stent System (XIENCE Sierra Stent System; P110019 / S094; approved on May 22, 2018)

All the above trial devices (hereinafter be called as "XIENCE" in the study) are manufactured by Abbott Vascular. The XIENCE Xpedition, XIENCE Alpine, and XIENCE Sierra EECSS have been approved by the Food and Drug Administration (FDA) and are currently in commercial use in the United States. These stent systems, the XIENCE PRO^{X} EECSS and the XIENCE PRO^{A} EECSS have also received Conformité Européene (CE) mark and are currently in commercial use in different European countries. Please refer to the Instructions for Use (IFU) for details of each stent system.

[10] XIENCE PRO^{X} is a rebrand of the XIENCE Xpedition Stent System and is only available outside of the U.S.
[11] XIENCE PRO^{A} is a rebrand of the XIENCE Alpine Stent System and is only available outside of the U.S.

2.2.2 Intended Indication for Use

The following is the proposed Intended Use/Indications for Use for the XIENCE Xpedition, XIENCE Alpine and XIENCE Sierra stent system in US as a result of the XIENCE 90 trial:

"The XIENCE [Xpedition/Alpine/Sierra] stent system is indicated for improving coronary artery luminal diameter in patients, including those ***at high risk for bleeding*** and those with diabetes mellitus, with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 32 mm) with reference vessel diameters of ≥ 2.25 mm to ≤ 4.25 mm. In addition, the XIENCE [Xpedition/Alpine/Sierra] stent system is indicated for treating *de novo* chronic total coronary occlusions."

2.2.3 Description of the Investigational Device

A full description of XIENCE Xpedition, XIENCE Alpine, XIENCE PRO^{X}, XIENCE PRO^{A} and XIENCE Sierra stent can be found in the individual stent IFU.

3.0 CLINICAL TRIAL/INVESTIGATION FLOW AND FOLLOW-UP SCHEDULE

3.1 [redacted]

[redacted]

3.2 Overall Flow of the Trial and Follow-up Schedule

The clinical investigation flow is shown in **Appendix V**. Subjects who satisfy eligibility criteria become registered in the study. Subjects have follow-up visits at 3, 6 and 12 months. Assessment of eligibility of DAPT discontinuation will occur at 3-month follow-up.

3.3 Measures Taken to Avoid and Minimize Bias

All the clinical endpoint events will be adjudicated by the Clinical Events Committee (CEC). The CEC is an independent adjudication body comprised of qualified physicians who are not participants in the trial. The CEC will review and adjudicate events as defined in the CEC charter and according to definitions provided in this protocol.

3.4 Early Termination of the Clinical Trial

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

The Sponsor reserves the right to discontinue the clinical trial/investigation at any stage or reduce the follow up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects.
- Any oversight committee (e.g., Steering/Executive Committee, Data Safety Monitoring Board [DSMB]) makes a recommendation to stop or terminate the trial (such as higher frequency of anticipated adverse device effects).
- Further product development is cancelled.

Should the clinical trial be discontinued by the Sponsor, subjects will be followed up as per routine hospital practice with device related AEs being reported to the Sponsor as per vigilance/commercial reporting requirements.

Should this occur, the investigator shall return all clinical trial/investigation materials to the Sponsor, and provide a written statement as to why the premature termination has taken place to the IRB/EC (if applicable). All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in **Section 12** Data Handling and Record Keeping.

4.0 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is a composite rate of all death or all myocardial infarction (MI, modified ARC) from 3 to 12 months. This composite endpoint was chosen because death and MI are important safety endpoints to evaluate short-term DAPT after PCI.

4.2 Major Secondary Endpoint(s)

- Major bleeding rate (BARC type 2-5) from 3 to 12 months
- Stent thrombosis (ARC definite/probable) from 3 to 12 months

4.3 Other Secondary Endpoint(s)

The following endpoints will be assessed from 3 to 12 months:

- All death, cardiac death, vascular death, non-cardiovascular death
- All MI (modified ARC) and MI attributed to target vessel (TV-MI, modified ARC)
- Composite of cardiac death or MI (modified ARC)
- All stroke, ischemic stroke and hemorrhagic stroke
- Clinically-indicated target lesion revascularization (CI-TLR)
- Clinically-indicated target vessel revascularization (CI-TVR)
- Target lesion failure (TLF, composite of cardiac death, TV-MI and CI-TLR)
- Target vessel failure (TVF, composite of cardiac death, TV-MI and CI-TVR)
- Major bleeding defined by the Bleeding Academic Research Consortium (BARC) type 3-5

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This trial will register male and female HBR subjects from the general interventional cardiology population who satisfy the inclusion and exclusion criteria. [redacted] Subjects must meet all clinical and angiographic eligibility criteria and provide written informed consent prior to conducting any trial-specific procedures not considered standard of care.

5.1.1 Medicare Population

This trial will register male and female HBR subjects including those age 65 years old and older, i.e., Medicare age. The study results are expected to be generalizable to the Medicare population. It is not expected that the results will be any different for Medicare patients than for non-Medicare patients.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Subjects admitted for a percutaneous coronary artery revascularization procedure must be screened for clinical trial eligibility by a member of the clinical trial team (physician and/or research coordinator) previously trained to the clinical trial protocol and if applicable will be entered into a site specific screening log.

Subjects meeting the general inclusion and exclusion criteria will be asked to sign an informed consent. Pre-procedure (or baseline) imaging will be used for the final assessment of subject eligibility (details are described in **Section 5.3**). Subjects who do not satisfy the angiographic inclusion and exclusion criteria are considered screen failures and will not be registered and proceed further in the trial. These subjects will be entered into the screening log. Also, the reason for screen failure as well as supporting data will be entered into the log.

Patient data will be collected following registration into the trial/investigation.

5.2.2 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 (and time, as per applicable local standards) the Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent (ICF) prior to any clinical trial/investigation-specific procedures. All efforts should be made to consent a subject prior to index procedure. However, it is acceptable for the subject to provide consent prior to hospital discharge and up to 3 days after the index procedure, only if the site confirms that the protocol required DAPT regimen is site's standard of care. If staged procedures are needed for a subject, the site may consent the subject after the initial procedure.

Obtaining the consent and provisioning of a copy to the subject, along with the date and time must be documented in the subject's medical records. The ICF must be signed by the investigator or designate (if allowed per country specific regulations). 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 subject's 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. The investigator must notify Abbott Vascular prior to performing a Live Case. FDA approval is also required for a live case conducted in US.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate subject. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is 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.

5.3.1.1 General Inclusion Criteria

1. Subject is considered at high risk for bleeding (HBR), defined as meeting one or more of the following criteria at the time of registration and in the opinion of the referring physician, the risk of major bleeding with > 3-month DAPT outweighs the benefit:
    a) ≥ 75 years of age.
    b) Clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy.
    c) History of major bleeding which required medical attention within 12 months of the index procedure.
    d) History of stroke (ischemic or hemorrhagic).
    e) Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent).
    f) Systemic conditions associated with an increased bleeding risk (e.g. hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk).
    g) Anemia with hemoglobin < 11g/dl.
2. Subject must be at least 18 years of age.
3. Subject or a legally authorized representative must provide written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site prior to any study related procedure.
4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at 3 months, if eligible per protocol.
5. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure.

5.3.1.2 General Exclusion Criteria

1. Subject with an indication for the index procedure of acute ST-segment elevation MI (STEMI).
2. Subject has a known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, P2Y12 inhibitors (clopidogrel/prasugrel/ticagrelor), everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated.
3. Subject with implantation of another drug-eluting stent (other than XIENCE) within 9 months prior to index procedure.
4. Subject has a known left ventricular ejection fraction (LVEF) <30%.
5. Subject judged by physician as inappropriate for discontinuation from P2Y12 inhibitor use at 3 months, due to another condition requiring chronic P2Y12 inhibitor use.

6. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 3 months following index procedure.
7. Subject with a current medical condition with a life expectancy of less than 12 months
8. Subject intends to participate in an investigational drug or device trial within 12 months following the index procedure.
9. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

   Note: Female patients of childbearing potential should be instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches, hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilised regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the study design, product characteristics and/or study population.

10. Subject is part of a vulnerable population, 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.
11. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.

5.3.2 Angiographic Eligibility Criteria

All angiographic eligibility criteria are based on visual assessment.

5.3.2.1 Angiographic Inclusion Criteria

1. Up to three target lesions with a maximum of two target lesions per epicardial vessel. Note:

   - The definition of epicardial vessels means left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX) and right coronary artery (RCA) and their branches. For example, the patient must not have >2 lesions requiring treatment within both the LAD and a diagonal branch in total.

- 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.

2. Target lesion ≤ 32 mm in length by visual estimation.
3. Target lesion must be located in a native coronary artery with visually estimated reference vessel diameter between 2.25 mm and 4.25 mm.
4. Exclusive use of XIENCE family of stent systems during the index procedure.
5. Target lesion has been treated successfully, which is defined as achievement of a final in-stent residual diameter stenosis of <20% with final TIMI-3 flow assessed by online quantitative angiography or visual estimation, 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 > 0.5 mm or depression lasting > 5 minutes.

5.3.2.2 Angiographic Exclusion Criteria

1. Target lesion is in a left main location.
2. Target lesion is located within an arterial or saphenous vein graft.
3. Target lesion is restenotic from a previous stent implantation.
4. Target lesion is a total occluded lesion (TIMI flow 0).
5. Target lesion contains thrombus as indicated in the angiographic images (per SYNTAX score thrombus definition).
6. Target lesion is implanted with overlapping stents, whether planned or for bailout.

Note: If there is more than one target lesion, all target lesions must satisfy the angiographic eligibility criteria. Non-target lesion (i.e., lesions that do not meet the angiographic criteria listed above) treatments are not allowed during the index procedure.

5.4 Subject Registration

Subject registration will occur after the index procedure but prior to discharge and up to 3 days post index procedure, upon confirmation of the following:

- Signed informed consent has been obtained;
- Subject has met all the inclusion and none of the exclusion criteria (including both general and angiographic criteria).

Planned staged procedures are allowed (recommend to be performed within 30 days). The site may consent the subject after the initial procedure. Subject registration will occur once the last staged procedure is performed, and the last staged procedure is considered as the index procedure.

5.5 Subject Discontinuation

All registered subjects will be considered to have completed the study upon study completion of the 12-month follow-up.

Each registered subject shall remain in the trial until completion of the required follow-up period; however, a subject's participation in any clinical trial 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 death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically-indicated
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to **Section 3.4** Early termination of the Clinical Trial

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will record this information on the eCRF and source documents and provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the trial, except for the status (deceased/alive).

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.

Lost-to-Follow-up:

If the subject misses two consecutive scheduled follow up time points and the attempts at contacting the subject 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 (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of 2 telephone calls on different days over the specified follow-up windows 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 letter (certified if applicable) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-study cardiologist or relative without presence of subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

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.

- If subject responds via written communication (including email correspondence), providing the protocol required data, these data will be collected in the case report form and the visit will not be considered a missed visit.

[redacted]

5.10 Trial Completion

A Trial Completion eCRF must be completed when:

- the subject is considered lost to follow-up per the above definition or
- the subject withdraws from the Clinical Trial or
- the investigator withdraws the subject from the Clinical Trial or
- the subject has died or
- upon Clinical Trial completion or
- sponsor termination of trial.

Sponsor must be notified of the reason for subject discontinuation. The site will provide this information on the eCRF. Investigators must also report this to their EC/IRB as defined by their institution's procedure. Subjects will not be replaced.

6.0 TREATMENT AND EVALUATION

6.1 Baseline and Pre-procedure

6.1.1 Laboratory Assessments

Baseline 12-lead electrocardiogram (ECG) and laboratory assessments (such as blood counts, chemistry panel and lipid panel, cardiac enzymes, etc.) should be obtained per site's standard of care. Baseline laboratory results related to inclusion/exclusion criteria should be available and reviewed prior to the index procedure for screening.

6.1.2 Clinical Assessments

Subject demographics (age, gender, race), height, weight, family history of coronary artery disease (CAD), smoking status, cardiac history (myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, and previous PCI/CABG information), subject's current cardiac status (presentation of CAD and multivessel disease) and indication of high bleeding risk (per criteria specified in **Section** 5.3.1.1) will be obtained and recorded in electronic case report form (eCRF).

6.1.3 Pre-procedure Antiplatelet Medication

Antiplatelet loading dose is required in this trial:

- Subjects must receive a loading dose of aspirin AND a P2Y12 inhibitor (Clopidogrel, Prasugrel or Ticagrelor). The dosages of aspirin and P2Y12 inhibitor shall be determined by physician per standard of care and label indication for loading dose usage. The choice of P2Y12 inhibitor is per site standard of care, but clopidogrel is strongly recommended for HBR subjects. Per physician's discretion, a loading dose of P2Y12 inhibitor may be omitted if the subject was on chronic usage for ≥ 7 days.

The details of the antiplatelet loading dose, including type of drug, dosage, date and time, will be recorded in eCRF.

6.2 Index Procedure

Only XIENCE stent can be used for target lesion(s). Stent implantation procedure should be performed according to the instruction for use (IFU) of the XIENCE family stent used. If XIENCE stent is delivered beyond the guide catheter but not implanted, the subject should not be registered in the study. If other DES was implanted, the subject should not be registered in the study.

In this study, a maximum of three target lesions may be treated with a maximum of two target lesions per epicardial vessel. Non-target lesion (i.e., lesions that do not meet the angiographic eligibility criteria) treatments are not allowed during the index procedure.

Planned staged procedures are allowed (recommend to be performed within 30 days). The site may consent the subject after the initial procedure. Subject registration will occur once the last staged procedure is performed and the last staged procedure is considered as the index procedure. Post-procedure DAPT duration will be measured from the last staged procedure. Any planned stenting procedure must be done prior to subject registration. The subject must not have any additional stenting procedure planned after the index procedure.

Subjects may receive appropriate anticoagulation and other therapy according to standard hospital practice.

Overlapping stents are not allowed in the study, whether planned or for bailout. Subjects who received overlapping stents should not be registered in this study.

Lesion characteristics (lesion location, % diameter stenosis, TIMI flow, RVD, lesion length, thrombus presence, bifurcation or not, lesion complexity), device (device name, size, number of device implanted, bailout usage, overlapping stent) and procedural information (procedure time, access site, procedural anticoagulant and anti-thrombotic medications, any procedure complications) will be collected and recorded in eCRF.

6.3 Post–procedure

6.3.1 Post-procedure Laboratory and Clinical Tests

Post-procedure ECG and cardiac enzymes are not mandatory in the study, and shall be performed per site's standard care. CK and CK-MB are preferred. If CK and CK-MB are not available, troponin should be collected.

6.3.2 Antiplatelet Medications during Follow-up

- All subjects must receive ≥75 to ≤100 mg of aspirin daily throughout the study. All subjects must maintain a minimum of 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most subjects*) or 90 mg twice daily of ticagrelor for at least 3 months following the procedure.
    - The choice of P2Y12 inhibitor is per site standard of care, but clopidogrel is strongly recommended for HBR subjects.

  - For subjects taking chronic anticoagulants, dual therapy (oral anticoagulant and a P2Y12 inhibitor, clopidogrel preferred) may be considered for the first 3 months after index procedure per investigator's discretion.

- At 3-month follow up, subject will be assessed for their eligibility of P2Y12 inhibitor discontinuation. Eligible subjects will discontinue P2Y12 inhibitor and receive ≥75 to ≤100 mg of aspirin daily through 1-year follow-up during the study if they are "3-month clear", defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

[redacted]

- Subjects who are not "3-month clear" are NOT eligible for P2Y12 inhibitor discontinuation at 3-month. These subjects will be treated per the investigator's discretion and will continue to be followed up through 12 months.

*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.

The use of the above antiplatelet medications, including the start and stop date, any changes, as well as the reason to stop, will be documented in the eCRF.

6.3.3 Other Chronic Concomitant Medications

Administration of concomitant medications other than any approved P2Y12 inhibitors and aspirin are not required in this protocol. Subjects may receive other medications as needed per physician's discretion.

6.4 Clinical Follow-up for All Subjects

Subjects registered in the trial will receive the following clinical follow-up:

- 3 months (90 ± 7 days): office visit (Note: A formal office visit is required at 3-month follow-up to ensure a thorough clinical evaluation. A telephone contact is an option only for subjects who would otherwise be lost to follow-up due to being unable to complete an office visit, but a formal follow-up visit is still preferred at 3 months.)
- 6 months (180 ± 14 days): office visit/ telephone contact (office visit is strongly recommended whenever possible)
- 12 months (365 ± 28 days): office visit/ telephone contact (office visit is strongly recommended whenever possible)

Clinical follow-up visits should be conducted by the investigator or study personnel who have been trained to the protocol. At 3-month follow-up visit, the investigator or designee

will assess whether the subject is "3-month clear" and eligible for P2Y12 inhibitor discontinuation per criteria defined in **Section 6.3.2**.

All registered subjects will be followed up through 12 months, regardless of eligibility to discontinue P2Y12 inhibitor.

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

- Any adverse events
- Use and compliance of protocol required antiplatelet medication
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)

Note that information obtained through indirect contacts with a subject's healthcare provider or immediate family member will NOT be considered as a study visit.

6.5 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 and recorded in eCRF:

- Any adverse events
- Use and compliance of protocol required antiplatelet medication
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)

If an unscheduled visit is conducted due to a suspected ischemic cardiac event, cardiac enzymes and ECG may be performed per site's standard care. CK and CK-MB are preferred. If CK and CK-MB are not available, troponin should be collected.

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).

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical trial adverse event reporting, AV has developed uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 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.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a 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.

7.1.3 Device Deficiency/Device Malfunction

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.

A device malfunction (DM) is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or the study protocol.

7.2 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, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated (Serious) Adverse Device Effect

Unanticipated (serious) adverse device effect [U(S)ADE] 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.

7.3 Adverse Event Reporting

7.3.1 Adverse Event Reporting

For all registered subjects, AE reporting starts when the guiding catheter enters the subject's vasculature. All AEs will be collected through 12-month follow-up visit.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be recorded on the AE eCRF page.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1) the investigator determined that the value is clinically significant,

2) the abnormal lab value required intervention, or

3) the abnormal lab value required subject termination from the study.

The Investigator will monitor the occurrence of AEs for each subject during the course of the clinical trial and report as required by this protocol in **Section 7** per AE and SAE definitions. AEs need to be collected as of the time point of guiding catheter enters the subject's vasculature on the appropriate AE eCRF form. Additional information with regards to an adverse event should be updated within the appropriate case report form.

A fax form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

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 became 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.

Serious adverse events that occurred in the user or persons other than the study subject should not be entered in the EDC system, however need to be reported via the SAE Notification Form.

The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 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.

7.3.3 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the EDC System on the appropriate eCRF form. A fax form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC. This

does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID has been assigned, the device deficiency should be reported to the Sponsor via the fax form.

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

Study sites	**Reporting timelines**
All Study Sites	DDs/DMs must be reported no later than 3 calendar days from the day the study personnel became 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 remaining in the subject, should be returned to Abbott Vascular.

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

If there is a device deficiency/malfunction related to other AV products, please contact the Product Performance Group (PPG) by e-mail: qahotline@av.abbott.com or contact AV Sales person to complete a Product Experience Form (PER Form).

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor or designee will report the SAEs and DDs/product experiences (PEs) to the country regulatory authority, per local requirements.

7.4 Safety Monitoring by Data Safety Monitoring Board (DSMB)

The DSMB will serve in an advisory role to Abbott Vascular to ensure safety by reviewing cumulative data from the clinical trial at prescribed intervals for the purpose of safeguarding the interests of trial participants.

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.

8.0 ADJUDICATION OF EVENTS

The Clinical Events Committee (CEC) is comprised of qualified physicians who are not investigators in the trial. The CEC will review and adjudicate pre-specified events reported by trial investigators or identified by the Clinical Safety personnel/designate for the trial as documented in CEC Manual of Operations (MOPs).

9.0 STATISTICAL ANALYSIS

9.1 Statistical Overview

The XIENCE 90 trial is powered based on primary endpoint of all death or all myocardial infarction [modified ARC] (Death/MI) from 3- to 12-month follow-up.

Primary endpoint analysis for 3-month DAPT

The primary endpoint of Death/MI between 3-month and 12-month follow-up will be evaluated based on the "3-month clear" population (as defined in section 9.2). [redacted]

9.2 Analysis Populations

The primary analysis population is "3-month clear" population, defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

9.3 [redacted]

9.4 Statistical Analyses

A stratified statistical method through propensity score will be used to test non-inferiority of 3-month DAPT in XIENCE 90 to XIENCE V USA historical control for the primary endpoint of death/MI at a 0.025 significant level.

Major secondary analyses will be performed only if the primary hypothesis testing is successful.

Analyses of other secondary endpoints and additional endpoints will be descriptive in nature.

For binary variables such as TLR, TVR, counts, percentages and 95% confidence intervals will be calculated, and p-values may be presented for hypothesis generating purposes. Pearson's Chi-squared test of Fisher's exact test will be performed when appropriate.

For continuous variables such as age, means, standard deviation, 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 Death/MI, 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).

9.4.1 Primary Endpoint Analysis

A non-inferiority test will be performed on the primary endpoint of Death/MI between 3-month and 12-month follow up for the "3-month clear" population of XIENCE 90 3-month DAPT arm and the XIENCE V USA historical control stratified by propensity scores.

Details of the analyses for the powered primary endpoint can be found in the Statistical Analysis Plan (SAP).

9.4.2 Major Secondary Endpoint Analysis

- Superiority will be tested for the major secondary endpoint of major bleeding (BARC type 2-5) between 3-month and 12-month follow up for the "3-month clear" population of XIENCE 90 3-month DAPT arm and the XIENCE V USA historical control stratified by propensity scores.
- Stent thrombosis (ARC definite/probable) from 3 to 12 months for the "3-month clear" population of XIENCE 90 will be evaluated against a pre-specified performance goal (PG).

9.4.3 Secondary Endpoint Analyses

Other secondary and additional clinical endpoints will be descriptively analyzed.

9.4.4 Subgroup Analysis

Analyses will be performed for subgroups such as gender (male versus female), diabetes (diabetes versus non-diabetes), ethnicity (white versus non-white), age (age ≥ median versus < median), clinical presentation (ACS NSTEMI, ACS unstable angina, non-ACS), and the subgroup of US elderly patient with age ≥ 65 years old.

9.4.5 Procedures for Accounting for Missing, Unused or Spurious Data

The primary and secondary endpoint analyses will be evaluated after propensity score stratification. To handle missing data, multiple imputation method will be performed to compute propensity scores from these datasets. For further details, refer to the SAP.

All other 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.

9.5 Deviations from the Original Statistical Plan

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

10.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order for clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections to be performed.

Subjects providing informed consent are agreeing to allow Sponsor and/or its designee access and copying rights to pertinent information in their medical records concerning their participation in this clinical investigation. The investigator will obtain, as part of the informed consent, permission for clinical investigation monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Selection of Clinical Sites and Investigators

Sponsor will select investigators qualified by training and experience, to participate in the investigation of the Clinical Investigation device. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the Primary Investigator or multidisciplinary team at the site.

11.2 Protocol Amendments

Approved protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Primary Investigator is responsible for notifying the IRB or equivalent committee of the protocol amendment (administrative changes) or obtaining IRB's approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Acknowledgement/approval by the IRB/EC of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

11.3 Training

11.3.1 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 or self-training may take place as required. Training of Investigators/trial personnel will include, but is not limited to, the Protocol requirements, 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.

11.3.2 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the Protocol and case report forms. Documentation of this training will be according to written procedures.

11.4 Monitoring

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

The Sponsor should be contacted for additional information on the person(s) responsible for monitoring activities.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will 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/her 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 (including original medical records) 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.

11.5 Deviations from the Protocol

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 rights, safety and 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 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 and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

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; Sponsor may terminate the investigator's participation in the study.

The following categories of protocol deviations will be considered as major:

- Informed Consent deviation
- Eligibility deviation
- Serious adverse event reporting deviation
- Treatment/procedure compliance deviation

The following categories of protocol deviations will be considered as minor:

- Data outside time window
- Missed visit

11.6 Quality Assurance Audits

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection and duplication during a Quality Assurance audit. In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

11.7 Committees

11.7.1 Steering Committee

The Steering Committee is assigned by the Sponsor and comprises the Principal Investigator as specified on the cover page of this Protocol, the Trial Chairman (if applicable) and four/five dedicated members from the trial sites. The Sponsor will be represented by at least one person each from the Clinical Science and Clinical Program Management groups. The Chairman 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 trial. This committee will meet regularly to monitor patient registration or randomization, general data collection and non-compliance with the trial 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 trial.

11.7.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group that is restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with relevant interventional experience (e.g., vascular surgeon, interventional radiologist, interventional cardiologist) and a biostatistician and is responsible for making recommendations regarding endpoint analyses and any potentially significant patient safety-related observations. The composition of the DSMB, frequency of the DSMB sessions and the statistical monitoring guidelines are described in detail in the DSMB charter. DSMB meeting minutes and recommendations are forwarded to Abbott Vascular.

In addition to an Abbott Vascular/designee safety monitor reviewing adverse events at regular intervals, a monthly listing of Adverse Events will be sent to the DSMB Chair or designee for review. If a safety signal is identified during this review, then the DSMB chair will call for an ad hoc full DSMB meeting.

11.7.3 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. The CEC will review and adjudicate events as defined in the CEC charter and according to definitions provided in this Protocol **Appendix II**.

12.0 DATA HANDLING AND RECORD KEEPING

Data Management will include documentation of the systems and procedures used in data collection for the duration of the trial.

All CRF 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. Passwords and electronic signatures will be strictly confidential.

All CRF 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.

At the conclusion of the trial, completed CRF 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 for each investigational 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 ICFs, device accountability records, correspondence with the IRB and clinical trial/investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical trial/investigation.

12.1 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's original 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 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 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 device relationship assessment of SAEs.
- Any laboratory reports and 12-lead ECGs (if performed), reviewed 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 CRF

12.2 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 subjects that are registered into the trial.

12.3 Record Retention

The Sponsor will archive and retain all documents pertaining to the trial as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical trial/investigation records.

13.0 ETHICAL CONSIDERATION

13.1 Institutional Review Board/Medical Ethics Committee Review

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the Protocol and ICF/other written information provided to the patient will be obtained by the Primary Investigator at each investigational site prior to participation in this clinical trial/investigation. The approval letter must be received 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 ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and/or the regulatory agencies.

Until the clinical trial/investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical trial/investigation, per IRB/EC requirements. Written approval

must be obtained from the IRB/EC yearly to continue the clinical trial/investigation, or according to each institution's IRB/EC requirements (US studies only). Further, any amendments to the Protocol as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC 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/EC and the Sponsor.

14.0 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 Sponsor will submit trial results for publication, regardless of trial outcome, following the conclusion or termination of the 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 Investigator intends to publish a multi-center publication regarding the clinical trial/investigation results. 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 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 ClinicalTrials.gov. Institution and/or Principal Investigator(s) shall not take any action to register the Trial.

15.0 RISK ANALYSIS

The optimal duration of DAPT remains a dilemma for clinicians with the current clinical practice, and is of particular interest to HBR patients which represent approximately 15% or more of patients undergoing PCI[22,23]. The default management of care for HBR patients who undergo PCI is often stenting with BMS followed by 1 month of DAPT. The European ESC/EACTS guidelines have recommended 3 months of DAPT with second-generation DES for HBR patients undergoing PCI[24]. Consistent with the European guideline, the updated 2016 ACC/AHA guideline also provided a class IIb recommendation of 3-month DAPT in SIHD patients with high risk of bleeding following DES implantation[17]. Studies with some DES (Endeavor, BioFreedom) have demonstrated safety of short-term DAPT for HBR patients[45,47].

XIENCE has consistently been shown to have the best safety profile among the coronary stents, even when compared to BMS, in both clinical trials and commercial data analysis. However, the benefit/risk ratio of a shorter duration of DAPT following XIENCE implantation in the HBR population has not been thoroughly evaluated. There is clearly an unmet medical need to be addressed for the HBR patient population as the possible benefits of extended DAPT therapy to prevent late stent thrombosis and the progression of

atherosclerotic disease need to be weighed against the increased risk of bleeding in an individual patient. Therefore, the XIENCE 90 study is designed to prospectively evaluate the safety of XIENCE followed with 3-month DAPT in HBR patients.

15.1 Anticipated Clinical Benefits

The excellent safety profile of XIENCE family of stents has been well demonstrated. Stent implantation and the following medical treatment are the same for subjects registered in this study as if they are not participating in this clinical study, except for DAPT duration. Short-term DAPT may decrease the risk of bleeding in HBR subjects. Participation of this study contributes to defining the optimum duration of DAPT in HBR subjects treated with XIENCE.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Observed and potential adverse events occurring with the XIENCE family of stents are listed in the IFUs. The incidence of these adverse events is comparable to other PCI devices. There may be risks related to the device that are unknown at present.

Please refer to the drug labelling (most recent versions available at www.fda.gov – drugs - drugs@fda and www.ema.europa.eu – find medicine – human medicines), and published guidelines on PCI and DAPT use[17,24] for information on bleeding and other risks associated with DAPT use.

Short-term DAPT use may decrease the risk of bleeding in HBR subjects, but may increase the risk of late stent thrombosis and progression of atherosclerotic disease.

15.3 Residual Risks Associated with the Investigational Device, as Identified in the Risk Analysis Report

The XIENCE Risk Assessment Report[12] utilizes the Failure Modes and Effects Analysis (FMEA) tool to systematically identify potential hazards associated with the process, design, components, and use of the XIENCE product family. Based upon preclinical, clinical, bench data, and commercial post-production data, all residual risks are appropriate and acceptable. The benefit of treatment from the XIENCE outweighs the potential risks to the patient.

Comprehensive analysis of product level clinical data, including clinical trial, post-marketing, and literature data, confirms that any undesirable risks identified are outweighed by the clinical benefits of the device[13] .

15.4 Risks Associated with Participation in Clinical Investigation

All procedures required by the protocol are routine standard of care. There are no additional risks to the subjects, except that short-term DAPT may increase the risk of stent thrombosis and ischemic events.

15.5 Possible Interactions with Protocol Required Concomitant Medications

Other than DAPT, the study protocol does not require concomitant medications.

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[12] RAM1070000 XIENCE Xpedition/XIENCE PRO^{x} EECSS RAM; RAM 1100000 XIENCE Alpine/XIENCE PRO^{A} EECSS RAM; RAM 1500000 XIENCE Sierra EECSS RAM

[13] RPT2098376 Rev G XIENCE EECSS Clinical Evaluation Report

15.6 Steps that will be Taken to Control or Mitigate the Risks

In-depth recommendations, special precautions and instructions regarding patient selection, vessel sizing, device handling, device placement and system removal are included in the IFU.

It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol, clinical follow-up by investigator or designee at pre-specified time points and the use of a DSMB.

All adverse events and device deficiencies observed in this study will be reported to Abbott Vascular, will be monitored internally for safety surveillance purposes, and will be reported to the regulatory authorities, as applicable (Refer to section 7.3 of this protocol).

Abbott Vascular updates the risk assessment reports and conducts comprehensive analysis of product level clinical data on a regular basis.

The XIENCE family of stents has not been tested in pregnant women. Effects on the developing fetus and excretion of everolimus in breast milk have not been studied. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure are excluded from participation in the clinical study. Female subjects of child-bearing potential must have a pregnancy test done within 7 days prior to the index procedure with negative results known to confirm eligibility prior to registration.

15.7 Risk to Benefit Rationale

The XIENCE family of stent has consistently been shown to have the best safety profile among the coronary stents, in both clinical trials and commercial data analysis. The optimal duration of DAPT remains a dilemma for clinicians with the current clinical practice, and is of particular interest to HBR patients which represent approximately 15% or more of patients undergoing PCI. The XIENCE 90 study is designed to prospectively evaluate the safety of XIENCE followed with 3-month DAPT in HBR patients. Reduced DAPT treatment duration may decrease the risk of bleeding, but may increase the risk of late stent thrombosis and progression of atherosclerotic disease, although studies with other DES have demonstrated safety of short-term DAPT for HBR patients. Other than a reduction in the duration of DAPT, all procedures required by the protocol are routine standard of care and conducted according to the current IFU.

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
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
BMS	Bare metal stents
CABG	coronary artery bypass graft
CAD	coronary artery disease
CASS	Coronary Artery Surgery Study
CCS	Canadian Cardiovascular Society (Canada)
CEC	Clinical Events Committee
CVA	Cerebrovascular Accident
CI	clinically-indicated
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase myocardial-band isoenzyme
CoCr-EES	cobalt chromium everolimus-eluting stent
CVA	cerebrovascular accident (or stroke)
DAPT	dual antiplatelet therapy
DD	device deficiency
DES	Drug-eluting stent
DM	device malfunction
DSMB	Data Safety Monitoring Board
EC	Ethics Committee (EU)
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EECS	everolimus eluting coronary stent
EECSS	everolimus eluting coronary stent system
FDA	Food and Drug Administration
FMEA	Failure Modes and Effects Analysis
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HBR	High bleeding risk
ICF	Informed Consent Form

Acronym or Abbreviation	Complete Phrase or Definition
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board (US and Japan)
KM	Kaplan-Meier
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
LMCA	left main coronary artery
LVEF	left ventricular ejection fraction
MACCE	major adverse cerebral and cardiovascular event
MEC	Medical Ethics Committee (EU)
MOP	Manual of Operations
µg	microgram
mg	milligram
MI	myocardial infarction
mL	milliliter
MLD	mean lumen diameter
mm	millimeter
N	sample size; also *N*
NSTEMI	non ST-segment elevation MI
NQMI	non-Q wave myocardial infarction
OCT	optical coherence tomography
OR	odds ratio
OUS	Outside of United States
PE	product experience
PCI	percutaneous coronary intervention
PG	performance goal
PTCA	percutaneous transluminal coronary angioplasty
QCA	quantitative coronary angiography
RCA	right coronary artery
RCT	randomized clinical trial
RVD	reference vessel diameter
RX	Rapid Exchange
SAE	serious adverse event
SAP	statistical analysis plan
SIHD	stable ischemic heart disease
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction

Acronym or Abbreviation	Complete Phrase or Definition
TLR	target lesion revascularization
TLF	target lesion failure
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

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:
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)

MI Definition (Modified ARC)

Patients present any of the following clinical or imaging evidence of ischemia:

- Clinical symptoms of ischemia;
- ECG changes indicative of new ischemia - new ST-T changes or new left bundle branch block (LBBB), development of pathological Q waves*;
- Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality)

AND confirmed with elevated cardiac biomarkers** per ARC criteria (Circulation 2007; 115: 2344-2351):

- Periprocedural MI:
  - Within 48h after PCI: CK-MB >3 x URL or Troponin > 3 x URL with baseline value < URL
  - Within 72h after CABG: CK-MB >5 x URL or Troponin > 5 x URL with baseline value < URL
- Spontaneous MI (> 48h following PCI, > 72h following CABG): CK-MB > URL or Troponin > URL with baseline value < URL

* Pathologic Q waves may be defined according to the Global Task Force, Minnesota code, or Novacode
** The assessment of CK-MB is preferred over the assessment of troponin for the diagnosis of peri-procedural MI, if possible. Baseline biomarker value requiring before study procedure and presumes a typical rise and fall.

Electrocardiographic Classification

- **Based on Q-Wave**
  - **Q-wave MI [QMI]**

- Development of new pathological Q waves in 2 or more contiguous leads with or without post- procedure CK or CK-MB levels elevated above normal.

- **Non Q-wave MI [NQMI]**
  - All MIs not classified as Q waves.

- **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.

WHO MI Definition
Myocardial infarctions will also be adjudicated based on the following 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

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

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)
- Non-occlusive thrombosis
  - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified 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.

STROKE

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

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

Note: an event that last < 24 hours may be adjudicated as a stroke if the following treatments were used:

- Pharmacologic, i.e., thrombolytic drug administration, or

Non-pharmacologic, i.e., neurointerventional procedure (e.g., intracranial angioplasty)

BLEEDING (Per BARC, Circulation 2011; 123: 2736-2747)
Bleeding will also be adjudicated per Bleeding Academic Research Consortium (BARC) definitions:

- Type 0: no bleeding
- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- Type 3
  - Type 3a
    - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - Type 3b
    - Overt bleeding plus hemoglobin drop ≥ 5 g/dL*(provided hemoglobin drop is related to bleed)
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive agents
  - Type 3c
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
    - Subcategories confirmed by autopsy or imaging or lumbar puncture
    - Intraocular bleed compromising vision
- Type 4: CABG-related bleeding
  - Perioperative intracranial bleeding within 48 h
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding
  - Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period†
  - Chest tube output ≥ 2L within a 24-h period
- Type 5: fatal bleeding
  - Type 5a
    - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
  - Type 5b
    - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
† Cell saver products are not counted.

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 clinically indicated [CI] or not clinically indicated by the investigator prior to repeat angiography. 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

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.

Clinically Indicated [CI] Revascularization (TLR/TVR)
A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥ 50% and if one of the following occurs:

- A positive history of recurrent angina pectoris, presumably related to the target vessel;
- Objective signs of ischemia at rest (ECG changes) or during 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% in the absence of the above mentioned ischemic signs or symptoms.

TARGET LESION FAILURE (TLF)
TLF is defined as a composite of all cardiac death, myocardial infarction attributed to target vessel or clinically-indicated TLR.

TARGET VESSEL FAILURE (TVF)

TVF is defined as a composite of cardiac death, MI attributed to target vessel, clinically-indicated TLR, or clinically-indicated TVR, non-TLR.

OTHER DEFINTIONS (in alphabetic order)

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
• Non-angulated 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

ACUTE CORONARY SYNDROME (ACS)

ACS is defined as ischemic symptoms occurring at rest and lasting 10 minutes or more and occurring within 72 hours before index procedure AND either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis (CK-MB or troponin T or I greater than the upper limit of normal.).

DE NOVO LESION

A native coronary artery lesion not previously treated.

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.

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.

MINIMUM LUMEN DIAMETER (MLD)
The average of 2 orthogonal views (when possible) of the narrowest point within the area of assessment, assessed by visual estimation or online QCA by the investigator.

PERCENT DIAMETER STENOSIS (% DS)
The value calculated by the following:
100 * (1 – minimum lumen diameter / reference vessel diameter)
using the mean values from 2 orthogonal views (when possible) assessed by visual estimation or online QCA by the investigator.

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/CIP 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.

REFERENCE VESSEL DIAMETER (RVD)
An approximation of the treated lesion vessel diameter. The reference vessel diameter is visually estimated during angiography or online QCA by the investigator.

STAGED PROCEDURE
A staged procedure is defined as the planned treatment of baseline lesions during one or more cardiac catheterization procedures following the initial procedure. Revascularization of the baseline lesions treated at the initial procedure is not considered a staged procedure.

TARGET LESION
The target lesion is defined as the lesion that has met the angiographic inclusion and exclusion criteria, and is implanted with XIENCE stent during the index procedure.

TARGET VESSEL
The entire epicardial vessel in which the target lesion is located, which includes upstream and downstream branches and the target lesion itself.

THROMBUS (PER SYNTAX SCORE DEFINITION)
Spheric, ovoid or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream.

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.

APPENDIX III: CONTACT INFORMATION

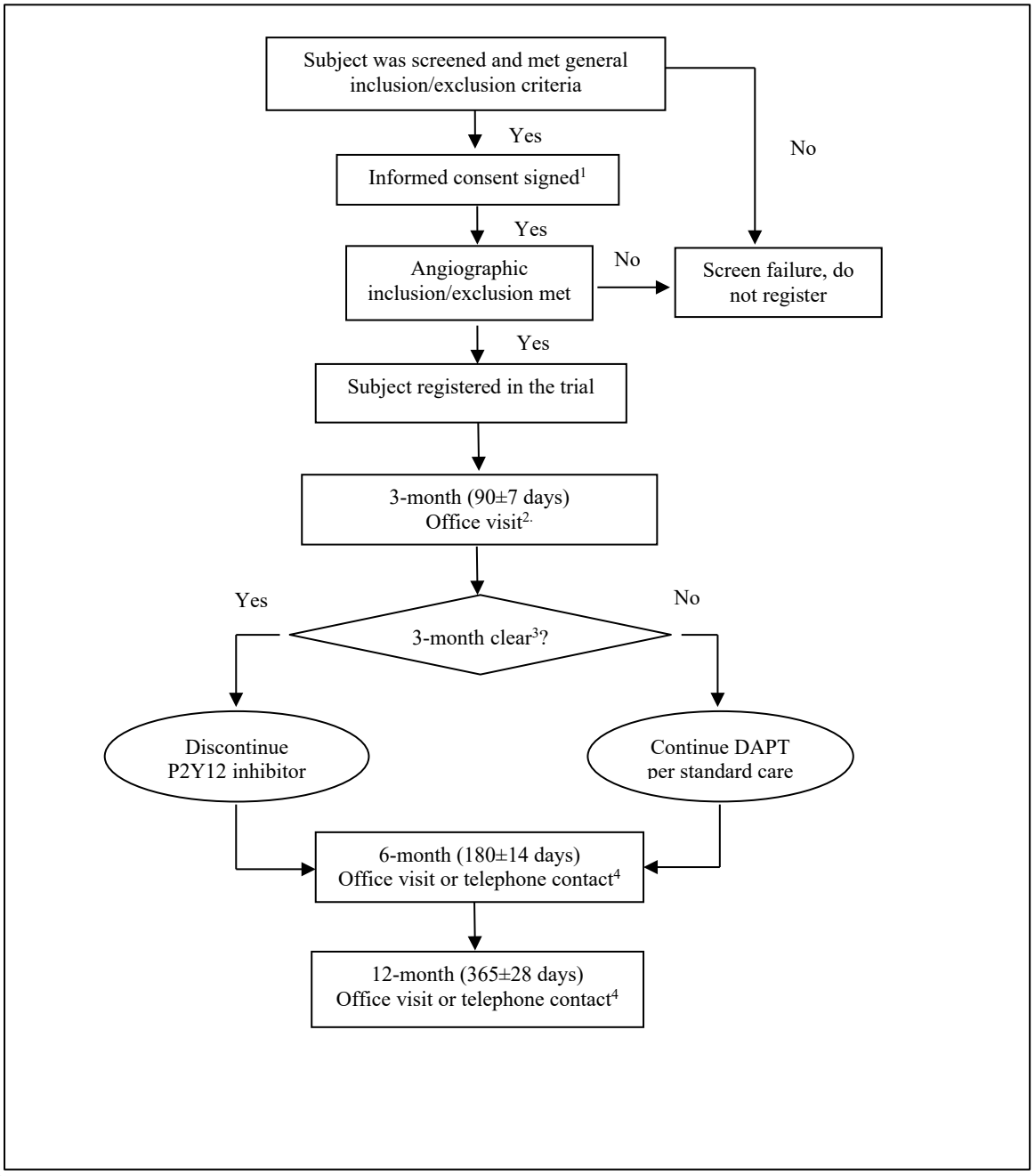
A list of investigational site co-ordinates can be obtained upon request from the Clinical Project Manager for the study.

APPENDIX IV: SCHEDULE OF EVENTS

PROCEDURE/TEST	Baseline	Pre-Procedure (within 24 hours)	Procedure	Post-Procedure	3-month (± 7d) Office visit[2]	6-month (± 14d) Office visit or phone contact [3]	12-month (± 28d) Office visit or phone contact[3]	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors, Cardiac 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			✓					
Coronary Angiogram			✓					
Study Stent and Procedure Information			✓					
Antiplatelet Medications Loading Dose		✓	✓					
P2Y12 Inhibitor Discontinuation Eligibility Assessment					✓			
Post-procedure Antiplatelet Medications[1]				✓	✓	✓	✓	✓
Adverse Events			✓	✓	✓	✓	✓	✓

[1]Subject who are "3-month clear" will discontinue P2Y12 inhibitor after 3-month visit, but continue taking aspirin through 12-month follow-up. Subjects who are not eligible for early P2Y12 inhibitor discontinuation will be treated per site standard of care.
[2]Office visit is required for 3-month follow-up. A formal office visit is required at 3-month follow-up to ensure a thorough clinical evaluation. A telephone contact is an option only for subjects who would otherwise be lost to follow-up due to being unable to complete an office visit, but a formal follow-up visit is still preferred at 3 months.
[3]Office visit is strongly recommended whenever possible.

APPENDIX V: CLINICAL INVESTIGATION FLOW



[1]Consenting after the index procedure but prior to hospital discharge (or up to 3 days after the index procedure) is acceptable, only if the site confirms that the protocol required DAPT regimen is site's standard of care. If staged procedures are needed for a subject, the site may consent the subject after the initial procedure.
[2]Office visit is required for 3-month follow-up. A formal office visit is required at 3-month follow-up to ensure a thorough clinical evaluation. A telephone contact is an option only for subjects who would otherwise be lost to follow-up due to being unable to complete an office visit, but a formal follow-up visit is still preferred at 3 months.
[3] "3-month clear" is defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting AND have been compliant with 3-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.
[4]Office visit is strongly recommended whenever possible.

APPENDIX VI: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Clinical Project Manager for the study.

APPENDIX VII: REFERENCES

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