PROTOCOL #ABT-CIP-10402
XIENCE 28 USA Study

Version Number	[redacted]
Date	December 4, 2018
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[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 and US Good Clinical Practice and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11 and 45 CFR part 46). The conduct of the trial will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

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PROTOCOL SUMMARY

Trial Name and Number	**XIENCE 28 USA Study: #ABT-CIP-10402**
Title	XIENCE 28 USA Study
Trial Device	The FDA 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 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 listed XIENCE stents will hereinafter be called "XIENCE" in this trial.
Objective	The objective of this trial is to evaluate safety of 1-month (as short as 28 days) 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 1 to 6 months following XIENCE implantation in HBR subjects treated with 1-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 1 to 6 months following XIENCE implantation in HBR subjects treated with 1-month DAPT compared to a historical control after propensity score adjustment.

[1] For each geography included in the trial (US and Canada), only approved and commercially available XIENCE stent(s) in that geography will be used.

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Clinical Trial Design	A prospective, single arm, multi-center, open label, non-randomized trial to evaluate the safety of 1-month (as short as 28 days) 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 [2]Academic Research Consortium [ARC]) from 1 to 6 months
Major Secondary Endpoints	Major bleeding rate (BARC type 2-5) from 1 to 6 months.
Secondary Endpoints	The following endpoints will be assessed from 1 to 6 months: • Stent thrombosis (ARC definite/probable, ARC definite) • All death, cardiac death, vascular death, non-cardiovascular death • All myocardial infarction (MI) and MI attributed to target vessel (TV-MI, modified ARC) • Composite of cardiac death or MI (modified ARC) • Composite of all death or all 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 The primary endpoint and major secondary endpoint, as well as the above secondary endpoints will also be assessed from 6 months to 12 months and from 1 month to 12 months.

[2] 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)

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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).
Subject Follow-Up	Subjects registered in the trial will receive the following clinical follow-up: • 1 month (28-35 days): office visit (Note: a formal office visit is required at 1-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 1-month.) • 3 months (90 ± 7 days): office visit/telephone contact (office visit is strongly recommended whenever possible) • 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 1-month DAPT, non-inferiority (NI) will be tested comparing 1-month DAPT to XIENCE V USA historical control for the primary endpoint of all death or all all MI (modified ARC) from 1- to 6-month follow-up in a "1-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 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days). [redacted]

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Major Secondary Analysis	Given the success of the primary analysis for the primary endpoint, the major secondary analysis will be performed pooling patients from the XIENCE 28 USA Study and the XIENCE 28 Global Study. A superiority test of major bleeding rate (BARC type 2-5) from 1- to 6-month follow-up will be tested against XIENCE V USA historical control stratified by propensity scores. Details of the major secondary analysis can be found in the Statistical Analysis Plan (SAP).
Antiplatelet Medication	**Antiplatelet Medication Loading Dose:** • Subjects must receive a loading dose of aspirin and/or 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. The loading of P2Y12 inhibitor can be omitted only if the subject is on chronic usage (≥ 7 days). Subjects that are not on chronic usage must be loaded with P2Y12 inhibitor. It is recommended that the subject be loaded with aspirin, even if the subject is on chronic usage of aspirin (≥ 7 days). **Antiplatelet Medication Post-Procedure Daily Dose:** • All subjects must receive ≥75 to ≤100 mg of aspirin daily throughout the trial. 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 1 month (as short as 28 days) following the procedure.

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	– 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 within the first month post index procedure per investigator's discretion. • At 1-month follow up, subject will be assessed for their eligibility of P2Y12 inhibitor discontinuation. Eligible subjects will discontinue P2Y12 inhibitor as early as 28 days and receive ≥75 to ≤100 mg of aspirin daily through 1-year follow-up during the trial if they are "1-month clear", defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days. Subjects who were on dual therapy during the first month (anticoagulant and a P2Y12 inhibitor) will discontinue the P2Y12 inhibitor after 1 month if they are assessed as "1-month clear". These subjects will start aspirin such that they will be on aspirin and anticoagulant for the remainder of the trial. If a subject was event-free and DAPT compliant (as defined above) during the first month, but does not stop P2Y12 inhibitor after the 1-month visit, due to physician's or subject's decision, this subject will be considered as "1-month not clear". If the physician judges that a 3-month DAPT duration, instead of 1-month duration, would be more appropriate for the subject, the physician has the option to transfer the subject to the XIENCE 90 study. This can only occur if the physician is an investigator in XIENCE 90 and if the subject was consented before the procedure. It is also 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. [redacted]

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	[redacted] • Subjects who are not "1-month clear" are NOT eligible for P2Y12 inhibitor discontinuation at 1-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 is allowed.
Cardiac Biomarker Collection	Cardiac biomarker CK, CK-MB and/or troponin collection shall be done per site's standard of care.
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 > 1-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 must provide written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site prior to any trial related procedure.

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	4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at 1 month, 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, except for cases where subject is transferred to the XIENCE 90 study after the 1-month visit assessment **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 subject 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 must be located in a native coronary artery with visually estimated reference vessel diameter between 2.25 mm and 4.25 mm. 3. Exclusive use of XIENCE family of stent systems during the index procedure. 4. 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 > 0.5mm 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).

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	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 12 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 1 month, due to another condition requiring chronic P2Y12 inhibitor use. 6. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 1 month 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. Transferring to the XIENCE 90 study will not be an exclusion criterion. 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 subjects 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 trial design, product characteristics and/or trial population 10. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with

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	follow-up requirements, or impact the scientific soundness of the clinical investigation results. 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 chronic total occlusion (CTO, defined as lesion with TIMI flow 0 for at least 3 months). 5. 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.
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. • Overlapping stents are not allowed in the trial, whether planned or for bailout. Subjects who received overlapping stents cannot be registered in this trial. According to XIENCE IFU, the maximal lesion length that may be treated is 32mm for a single XIENCE stent. • Bifurcation lesions are allowed in this trial. However, subjects treated with double stenting of both the main vessel and the side branch cannot be registered in this trial. • Planned staged procedures are not allowed
Primary Analysis Population	The primary analysis population includes “1-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 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

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	The above defined "1-month clear" population will be pooled from the XIENCE 28 USA Study and XIENCE 28 Global Study for both the primary and major secondary analyses.

1.0 INTRODUCTION

1.1 Trial Design

XIENCE 28 USA Study is a prospective, single arm, multi-center, open label trial to evaluate the safety of 1-month (as short as 28 days) 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 FDA approved XIENCE Xpedition Everolimus Eluting Coronary Stent System (EECSS), XIENCE Alpine EECSS and XIENCE Sierra EECSS which are all manufactured by Abbott Vascular, Inc. The above listed XIENCE stents will hereinafter be called "XIENCE" in this trial. For each geography included in the trial (US and Canada), only approved and commercially available XIENCE stent(s) in that geography will be used.

[redacted] Trial 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 1-month follow-up. Subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month DAPT without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days are considered as "1-month clear", and will discontinue P2Y12 receptor inhibitor as early as 28 days and continued with aspirin monotherapy through 12-month follow-up.

All registered subjects will be followed at 1, 3, 6 and 12 months post index procedure.

The data collected from the XIENCE 28 USA Study will be pooled with the data from the XIENCE 28 Global Study (Protocol # ABT-CIP-10235) to compare 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. The XIENCE V USA Study has been completed with a total of 8040 subjects enrolled, of which, ~1400 subjects were identified as non-complex HBR subjects who match the selection criteria of the XIENCE 28 USA Study. The XIENCE 28 Global Study is another AV-sponsored prospective, single arm study to evaluate the safety of 1-month DAPT in HBR subjects undergoing PCI with XIENCE. The XIENCE 28 Global Study is currently ongoing [redacted]. The XIENCE 28 Global Study and the current XIENCE 28 USA Study share similar study design regarding inclusion/exclusion criteria, DAPT treatment strategy and follow up schedule, which supports the pooling of the two trial results.

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1.2 Trial Objective

The objective of this trial is to evaluate safety of 1-month (as short as 28 days) 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 1 to 6 months following XIENCE implantation in HBR subjects treated with 1-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 1 to 6 months following XIENCE implantation in HBR subjects treated with 1-month DAPT compared to a historical control after propensity score adjustment.

2.0 BACKGROUND INFORMATION

2.1 Background and Rationale

Long-term dual antiplatelet therapy (DAPT) is known to increase the risk of bleeding. Multiple studies have demonstrated the relationship between bleeding and an increased risk of short- and long-term mortality[3,4], with major bleeding being identified as an independent predictor of mortality with a weight similar to or even greater than myocardial infarction (MI)[5]. A recent meta-analysis by Palmerini with 12 trials comprising > 34,000 patients randomized to different duration strategies of DAPT showed 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[6]. This important finding underlies the most important benefit with short-term DAPT, which is especially relevant for patients who are at high risk of bleeding (HBR).

HBR patients represent approximately 15% or more of the current percutaneous coronary intervention (PCI) population.[7,8] This patient population is of a significant size but is usually

[3] Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC. Cardiovascular interventions.* Jun 2011;4(6):654-664

[4] Pocock SJ, Mehran R, Clayton TC, et al. Prognostic modeling of individual patient risk and mortality impact of ischemic and hemorrhagic complications: assessment from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation.* Jan 05 2010;121(1):43-51

[5] Genereux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *Journal of the American College of Cardiology.* Sep 01 2015;66(9):1036-1045

[6] Palmerini T, Bacchi Reggiani L, Della Riva D, et al. Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting. *Journal of the American College of Cardiology.* Apr 25 2017;69(16):2011-2022

[7] Morice MC, et al. Why are we still using coronary bare-metal stents? *Journal of the American College of Cardiology.* Mar 12 2013;61(10):1122-1123

[8] Urban P, et al. Rationale and design of the LEADERS FREE trial: A randomized double-blind comparison of the BioFreedom drug-coated stent vs the Gazelle bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy. *Am Heart J.* May 2013;165(5):704-709.

underrepresented from traditional drug eluting stent (DES) trials. The optimal duration of DAPT for HBR subjects is yet to be determined. For some HBR patients, prolonging DAPT even beyond one month may be detrimental and hazardous. This is a challenging patient cohort requiring a trial designed to further optimize their therapy needs for DAPT after coronary revascularization. Given the lack of specific data in this arena for DES, the current ACC/AHA guidelines recommend use of bare metal stent (BMS) with 1-month DAPT [9]. 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 a DES followed by a shortened course of DAPT may represent a more favorable treatment option if there is no significant increase in ischemic events.

There is limited clinical data with 1 month DAPT after DES in HBR population. 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.[10] A total of 2,466 HBR patients were randomized in a 1:1 ratio to BioFreedom or a similar BMS (Gazelle). The primary safety endpoint, tested for both noninferiority and superiority, was a composite of cardiac death, MI, or stent thrombosis (definite/probable). The primary efficacy endpoint was clinically driven target lesion revascularization (CD-TLR). At 1 year, the rate of the composite endpoint of cardiac death, MI, or stent thrombosis was significantly lower 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%, $p = 0.75$). Consistent results were also demonstrated in a pre-specified HBR subgroup analysis from ZEUS trial with 1-month DAPT, which showed favorable outcomes with Endeavor group versus BMS group. In this HBR substudy, MACE (death, MI, or target vessel revascularization) occurred in 22.6% of the Endeavor group and 29% of the BMS group with a hazard ratio 0.75 ($p=0.033$) [11]. The definite or probable ST was also significantly reduced in the Endeavor group (2.6% vs. 6.2%, $p=0.016$). Results from both ZEUS and LEADER FREE suggest that DES can be a safer choice for HBR patients than BMS with short duration of DAPT. Based on these data, the most recent 2017 ESC guideline recommended 3-month DAPT (Class IIa) in high bleeding risk patients with stable CAD and 1-month DAPT (Class IIb) for those patients in whom 3-month DAPT poses safety concerns.[12]

The second generation XIENCE everolimus-eluting stent (EES) has been the subject of extensive clinical studies. Consistently low late and very late stent thrombosis rates have been reported with EES from randomized controlled studies as well as real-world registry studies. Results from several recent large scale meta-analyses demonstrated that EES has a better

[9] Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. *Circulation.* 2016 134 (10): e123-55
[10] Urban P, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* Nov 19 2015;373(21):2038-2047
[11] Ariotti S, et al. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A pre-specified analysis from the ZEUS trial. JACC Cardiovascular Interventions 2016; 9 (5): 426-436
[12] Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Heart Journal (2017) doi:10.1093/eurheartj/ehx419

[redacted]

safety profile than BMS and other DES,[13,14] even in complex patient groups who are known at high risk of ischemic events such as diabetes and STEMI.[15,16 17] The excellent safety profile of XIENCE is likely attributed to the unique combination of its thin struts (81 μm), the thromboresistant nature of the biocompatible fluoropolymer, and a low loading dose and release kinetics of the anti-proliferative agent, everolimus. The unique combination of the specific design features in XIENCE may lead to a more rapid endothelial coverage of strut surface and faster arterial healing compared with the other DES. Pre-clinical studies of endothelialization demonstrated that XIENCE V had a faster rate of strut coverage following stent implantation than Endeavor,[18] and was equivalent to BioFreedom.[19] 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[20], which showed 93.6% strut coverage at 1 month and 98% strut coverage at 3 months in subjects with stable coronary artery disease receiving XIENCE V. Additionally, XIENCE showed a significant reduction in platelet adherence compared to BioFreedom stents in *ex vivo* studies[21]. Given the large body of both pre-clinical and clinical evidence on the safety of the XIENCE DES platform, XIENCE is believed to be a safe and effective DES option for HBR population with 1-month DAPT.

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 versus risk of 1-month DAPT following XIENCE implantation in this population has not been prospectively evaluated. The XIENCE 28 USA Study will evaluate this important clinical question in a carefully controlled study setting. The results of the trial could potentially provide a definitive answer for the physicians as to the treatment of HBR patients with a safe and effective DES option.

[13] Palmerini T, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet.* Apr 14 2012;379(9824):1393-1402
[14] Bangalore S, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ. 2013;347:f6625
[15] Bangalore S, et al. Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22844 patient years of follow-up from randomized trails. BMJ 2012;345:e5170 doi: 10.1136/bmj.e5170 (Published 10 August 2012)
[16] Bangalore S, et al. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circ Cardiovasc Interv. 2013 Aug;6(4):378-90
[17] Palmerini T, et al. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction. Evidence from a comprehensive network meta-analysis. JACC 2013; 62 (6): 496-504
[18] Joner M, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *Journal of the American College of Cardiology.* Jul 29 2008;52(5):333-342
[19] Yazdani S, et al. Endothelialization of polymers-free drug coated stents. *EuroIntervention.* 2011;7(Supplement M)
[20] Shinke T, Itoh T, Ishida M, et al. Early vascular responses to everolimus-eluting cobalt-chromium stent for the treatment of stable coronary artery disease: The results of MECHANISM-Elective 1 and 3 months OCT follow-up cohort. ESC; 2016
[21] Data on file with Abbott Vascular

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2.2 Device Overview

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 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. For each geography included in the trial (US and Canada), only approved and commercially available XIENCE stent(s) in that geography will be used.

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 as a result of the XIENCE 28 USA 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 and XIENCE Sierra stent systems can be found in the individual stent IFU.

3.0 CLINICAL TRIAL FLOW AND FOLLOW-UP SCHEDULE

[redacted]

3.2 Overall Flow of the Trial and Follow-up Schedule

The clinical trial flow is shown in **Appendix V**. Subjects who satisfy eligibility criteria become registered in the trial. Subjects have follow-up visits at 1, 3, 6 and 12 months. Assessment of eligibility of DAPT discontinuation will be performed at 1-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.

[redacted]

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 at any stage or reduce the follow up period with suitable written notice to the investigator and authorities. 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 materials to the Sponsor, and provide a written statement as to why the premature termination has taken place to the IRB (if applicable). All applicable clinical trial 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 1 to 6 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

The major secondary endoint is major bleeding rate (BARC type 2-5) from 1 to 6 months.

4.3 Secondary Endpoint(s)

The following endpoints will be assessed from 1 to 6 months:

- Stent thrombosis (ARC definite/probable, ARC definite)
- All death, cardiac death, vascular death, non-cardiovascular death
- All myocardial infarction (MI) and MI attributed to target vessel (TV-MI, modified ARC)
- Composite of cardiac death or MI (modified ARC)
- Composite of all death or all MI (modified ARC)
- All stroke, ischemic stroke and hemorrhagic stroke
- Clinically-indicated target lesion revascularization (CI-TLR)

[redacted]

- 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

The primary endpoint and the major secondary endpoint, as well as all the above secondary endpoints will also be assessed from 6 months to 12 months and from 1 month to 12 months.

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.

Subject data will be collected following registration into the trial.

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 must sign and date the Institutional Review Board (IRB) approved informed consent (ICF) prior to any clinical trial-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.

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. 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.

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.

For Live cases at congresses the patients need to sign a specific Live Case ICF, approved by the IRB. 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 > 1-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.

[redacted]

3. Subject must provide written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site prior to any trial related procedure.
4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at 1 month, 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, except for cases where subject is transferred to the XIENCE 90 study after the 1-month visit assessment.

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 12 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 1 month, due to another condition requiring chronic P2Y12 inhibitor use.
6. Subject with planned surgery or procedure necessitating discontinuation of P2Y12 inhibitor within 1 month 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. Transferring to the XIENCE 90 study will not be an exlusion criterion.
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 subjects 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 trial design, product characteristics and/or trial population.

[redacted]

10. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.
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 subject 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 must be located in a native coronary artery with visually estimated reference vessel diameter between 2.25 mm and 4.25 mm.
3. Exclusive use of XIENCE family of stent systems during the index procedure.
4. 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 > 0.5mm 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 chronic total occlusion (CTO, defined as lesion with TIMI flow 0 for at least 3 months).
5. Target lesion is implanted with overlapping stents, whether planned or for bailout.

[redacted]

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 completion of successful index procedure (see "Angiographic Inclusion Criteria" above for definition of successful treatment of target lesion) 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).

5.5 Subject Discontinuation

All registered subjects will be considered to have completed the trial upon trial 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 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 trial due to problems related to the device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical trial.

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:

[redacted]

- 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-trial 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.

[redacted]

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 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

Subjects must receive a loading dose of aspirin and/or 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. The loading of P2Y12 inhibitor can be omitted only if the subject is on chronic usage (≥ 7 days). Subjects that are not on chronic usage must be loaded with P2Y12 inhibitor. It is recommended that the subject be loaded with aspirin, even if the subject is on chronic usage of aspirin (≥ 7 days).

The details of the antiplatelet loading dose, including type of drug, dosage, date and time, will be recorded in eCRF. In addition, whether the subject is taking oral anticoagulants will also be collected.

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 cannot be registered in the trial. If other DES was implanted, the subject cannot be registered in the trial.

In this trial, 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.

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

[redacted]

Overlapping stents are not allowed in the trial, whether planned or for bailout. Subjects who received overlapping stents cannot be registered in this trial. According to XIENCE IFU, the maximal lesion length that may be treated is 32mm for a single XIENCE stent.

Bifurcation lesions are allowed in this trial. However, subjects treated with double stenting of both the main vessel and the side branch cannot be registered in this trial.

Planned staged procedures are not allowed.

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 trial, and shall be performed per site's standard care.

6.3.2 Antiplatelet Medications during Follow-up

- All subjects must receive ≥75 to ≤100 mg of aspirin daily throughout the trial. 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 1 month (as short as 28 days) 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 within the first month post index procedure per investigator's discretion.
- At 1-month follow up, subject will be assessed for their eligibility of P2Y12 inhibitor discontinuation. Eligible subjects will discontinue P2Y12 inhibitor as early as 28 days and receive ≥75 to ≤100 mg of aspirin daily through 1-year follow-up during the trial if they are "1-month clear", defined as subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite/probable) within 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days. Subjects who were on dual therapy during the first month (anticoagulant and a P2Y12 inhibitor) will discontinue the P2Y12 inhibitor after 1 month if they are assessed as "1-month clear". These subjects will start aspirin such that they will be on aspirin and anticoagulant for the remainder of the trial.

  If a subject was event-free and DAPT compliant (as defined above) during the first month, but does not stop P2Y12 inhibitor after the 1-month visit, due to physician's or subject's decision, this subject will be considered as "1-month not clear". If the physician

judges that a 3-month DAPT duration, instead of 1-month duration, would be more appropriate for the subject, the physician has the option to transfer the subject to the XIENCE 90 study. This can only occur if the physician is an investigator in XIENCE 90 and if the subject was consented before the procedure. It is also 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.

[redacted]

- Subjects who are not "1-month clear" are NOT eligible for P2Y12 inhibitor discontinuation at 1-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 is allowed.

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:

- 1 month (28-35 days): office visit (Note: a formal office visit is required at 1-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 1-month.)
- 3 months (90 ± 7 days): office visit/telephone contact (office visit is strongly recommended whenever possible)
- 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 trial personnel who have been trained to the protocol. At 1-month follow-up visit, the investigator or designee will

[redacted]

assess whether the subject is "1-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 trial 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.

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 medical device.

Note 1: This definition includes events related to the 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 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 product, whether or not related to the medicinal product.

[redacted]

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.

5) Resulted in chronic disease

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 Study 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 trial protocol.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that a product or device caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate eCRF form. For clinical endpoint events that are sent to the CEC for adjudication, event relatedness to the study device will also be adjudicated by the CEC. The CEC members will be trained on the criteria used for determination of device relationship. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, and medical/biologic plausibility.

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 study 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 6-month follow-up visit. After 6 months, only the following will be collected in those subjects:

- All serious AEs
- All cardiovascular events regardless of seriousness or device relationship
- All trial device-related events and events for which the relationship to the trial device is unknown
- All Cerebrovascular Accident (CVA) and bleeding complications

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 trial.

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 (TPT2117940) 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.

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

[redacted]

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 trial subject should not be entered in the EDC system, however need to be reported via the SAE Notification Form (TPT2117940).

The Investigator will further report the SAE to the local IRB according to the institution's IRB 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 per IRB 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 (FRM 2015541-ABT) 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 (FRM 2015541-ABT).

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

Trial sites	**Reporting timelines**
All Trial Sites	DDs/DMs must be reported no later than 3 calendar days from the day the trial personnel became aware of the event or as per the trial 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 per the trial 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.

[redacted]

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 ANALYSES

9.1 Statistical Overview

The XIENCE 28 USA Study is powered based on primary endpoint of all death or all myocardial infarction [modified ARC] (Death/MI) from 1- to 6-month follow-up.

Primary endpoint analysis for 1-month DAPT

The primary endpoint of Death/MI between 1-month and 6-month follow-up will be evaluated based on the "1-month clear" population (as defined in section 9.2) pooled from the XIENCE 28 USA Study and XIENCE 28 Global Study. [redacted]

9.2 Analysis Populations

The primary analysis population includes "1-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 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month dual antiplatelet therapy (DAPT) without interruption of either aspirin and/or P2Y12 receptor inhibitor for > 7 consecutive days.

If a subject was event-free and DAPT compliant (as defined above) during the first month, but does not stop P2Y12 inhibitor after the 1-month visit, due to physician's or subject's decision, this subject will be considered as "1-month not clear".

[redacted]

The above defined "1-month clear" population will be pooled from the XIENCE 28 USA Study and XIENCE 28 Global Study for both the primary and major secondary analyses.

[redacted]

9.4 Statistical Analyses

A stratified statistical method through propensity score will be used to test non-inferiority of 1-month DAPT to XIENCE V USA historical control for the primary endpoint of death/MI at a 0.025 significant level.

Major secondary analysis 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.

[redacted]

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 trial sites.

For further details refer to the SAP.

9.4.1 Primary Endpoint Analysis

A non-inferiority test will be performed on the primary endpoint of Death/MI between 1-month and 6-month follow up for the "1-month clear" population (pooled from XIENCE 28 USA Study and XIENCE 28 Global Study) and the XIENCE V USA historical control stratified by propensity scores.

Details of the analysis for the powered primary endpoint can be found in the 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 1-month and 6-month follow up for the "1-month clear" population (pooled from XIENCE 28 USA Study and XIENCE 28 Global Study) and the XIENCE V USA historical control stratified by propensity scores.

Details of the analysis for the major secondary endpoint can be found in the SAP.

9.4.3 Secondary Endpoint Analyses

Other secondary and additional clinical endpoints will be descriptively analyzed.

9.4.4 Poolability Analyses

Poolability analyses will be conducted to evaluate the geography/study effect, as well as the center effect, on the primary endpoint. Further details on poolability analyses can be found in the Statistical Analysis Plan.

9.4.5 Subgroup Analysis

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

9.4.6 Procedures for Accounting for Missing, Unused or Spurious Data

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.

[redacted]

10.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents in order for clinical trial-related monitoring, audits, IRB 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 trial. The investigator will obtain, as part of the informed consent, permission for clinical trial monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this clinical trial. 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 trial. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the Principal 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 Principal 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 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 trial over its duration according to the pre-specified monitoring plan which will include the planned extent of source data verification.

[redacted]

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 trial according to the Protocol and applicable regulations, and has signed the Investigator Agreement.
- The Investigator and his/her staff have sufficient time and facilities to conduct the trial and that they have access to an adequate number of appropriate subjects to conduct the trial.
- 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 trial monitor with a suitable working environment for review of trial-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 or equivalent committee of all Protocol deviations in accordance with their specific IRB 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 trial 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 trial.

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

[redacted]

- 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 trial 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 trial , 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 trial (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 Study Principal Investigator, the Study Co-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 trial site and a backup copy archived with Abbott Vascular.

For the clinical trial duration, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical trial progress records, laboratory reports, electronic case report forms, signed ICFs, device accountability records, correspondence with IRB and clinical trial monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical trial.

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 trial:

- 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 Review

Institutional Review Board (IRB) approval for the Protocol and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each trial site prior to participation in this clinical trial. The approval letter must be received prior to the start of this clinical trial 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, the Sponsor, and/or the regulatory agencies.

Until the clinical trial is completed, the Investigator will advise his/her IRB of the progress of this clinical trial, per IRB requirements. Further, any amendments to the Protocol as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to each institution's IRB 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 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 related data without the written consent of the Sponsor for any other purpose than for Clinical trial completion or for generation of publication material, as referenced in the Clinical trial Site Agreement. The publication and/or presentation of results from a single clinical trial site are not allowed until publication and/or presentation of the multi-center results. The Sponsor acknowledges that the Study Principal Investigator intends to publish a multi-center publication regarding the clinical trial 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 Site Agreement.

Upon receiving IDE approval from the FDA, this clinical trial will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website no later than 12-months after clinical trial completion, as required by section 801 of the FDA Amendments Act. If this clinical trial is terminated early for safety, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

15.0 RISK ANALYSIS

The optimal duration of DAPT remains under debate 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 default management of care for HBR patients who undergo PCI is often stenting with BMS followed by 1 month of DAPT. 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[22]. The most recent 2017 ESC guideline recommended 3-month DAPT (Class IIa) in high bleeding risk patients with stable CAD and 1-month DAPT (Class IIb) for those patients in whom 3-month DAPT poses safety concerns.[23]

XIENCE has consistently been shown to have the best safety profile among the coronary stents, even when compared to BMS. 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 28 USA Study is designed to prospectively evaluate the safety of XIENCE followed with 1-month (as short as 28 days) 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

[22] Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. *Circulation.* 2016 134 (10): e123-55

[23] Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Heart Journal (2017) doi:10.1093/eurheartj/ehx419

[redacted]

trial as if they are not participating in this clinical trial, except for DAPT duration. One-month DAPT may decrease the risk of bleeding in HBR subjects. Participation of this trial 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 at www.fda.gov – drugs - drugs@fda), and published guidelines on PCI and DAPT use for information on bleeding and other risks associated with DAPT use.

One-month DAPT 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 Device, as Identified in the Risk Analysis Report

The XIENCE Risk Assessment Report[24] 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[25] .

15.4 Risks Associated with Participation in Clinical Trial

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

15.5 Possible Interactions with Protocol Required Concomitant Medications

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

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.

[24] RAM1070000 XIENCE Xpedition EECSS RAM; RAM 1100000 XIENCE Alpine EECSS RAM; RAM1500000 XIENCE Sierra EECSS RAM

[25] RPT2098376 Rev G XIENCE EECSS Clinical Evaluation Report

[redacted]

Risks associated with the use of the device during this clinical trial are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, trial 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 trial will be reported to Abbott Vascular, will be monitored internally for safety surveillance purposes, and will be reported to the regulatory authorities, as applicable.

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 trial. 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. The optimal duration of DAPT remains under debate 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 28 USA Study is designed to prospectively evaluate the safety of XIENCE followed with 1-month (as short as 28 days) 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 confirmed safety of 1-month DAPT for HBR patients[26,27]. Other than a reduction in the duration of DAPT, all procedures required by the protocol are routine standard of care, conducted according to current IFU.

[26] Urban P, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med.* Nov 19 2015;373(21):2038-2047

[27] Ariotti S, et al. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A pre-specified analysis from the ZEUS trial. JACC Cardiovascular Interventions 2016; 9 (5): 426-436

[redacted]

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
CTO	Chronic total occlusion
CVA	cerebrovascular accident (or stroke)
DAPT	dual antiplatelet therapy
DD	device deficiency
DES	Drug-eluting stent
DM	device malfunction
DSMB	Data Safety Monitoring Board
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

Acronym or Abbreviation	Complete Phrase or Definition
HBR	High bleeding risk
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
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
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

[redacted]

Acronym or Abbreviation	Complete Phrase or Definition
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
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

[redacted]

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

[redacted]

- **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

[redacted]

- 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.

[redacted]

- 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

[redacted]

- 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 (ie, 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.

[redacted]

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

[redacted]

- 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.

STUDY 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.

PRINCIPAL INVESTIGATOR
A physician responsible for conducting the clinical trial at each trial 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.

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.

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.

[redacted]

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.

[redacted]

APPENDIX III: CONTACT INFORMATION

A list of trial site coordinators can be obtained upon request from the Clinical Project Manager for the trial.

[redacted]

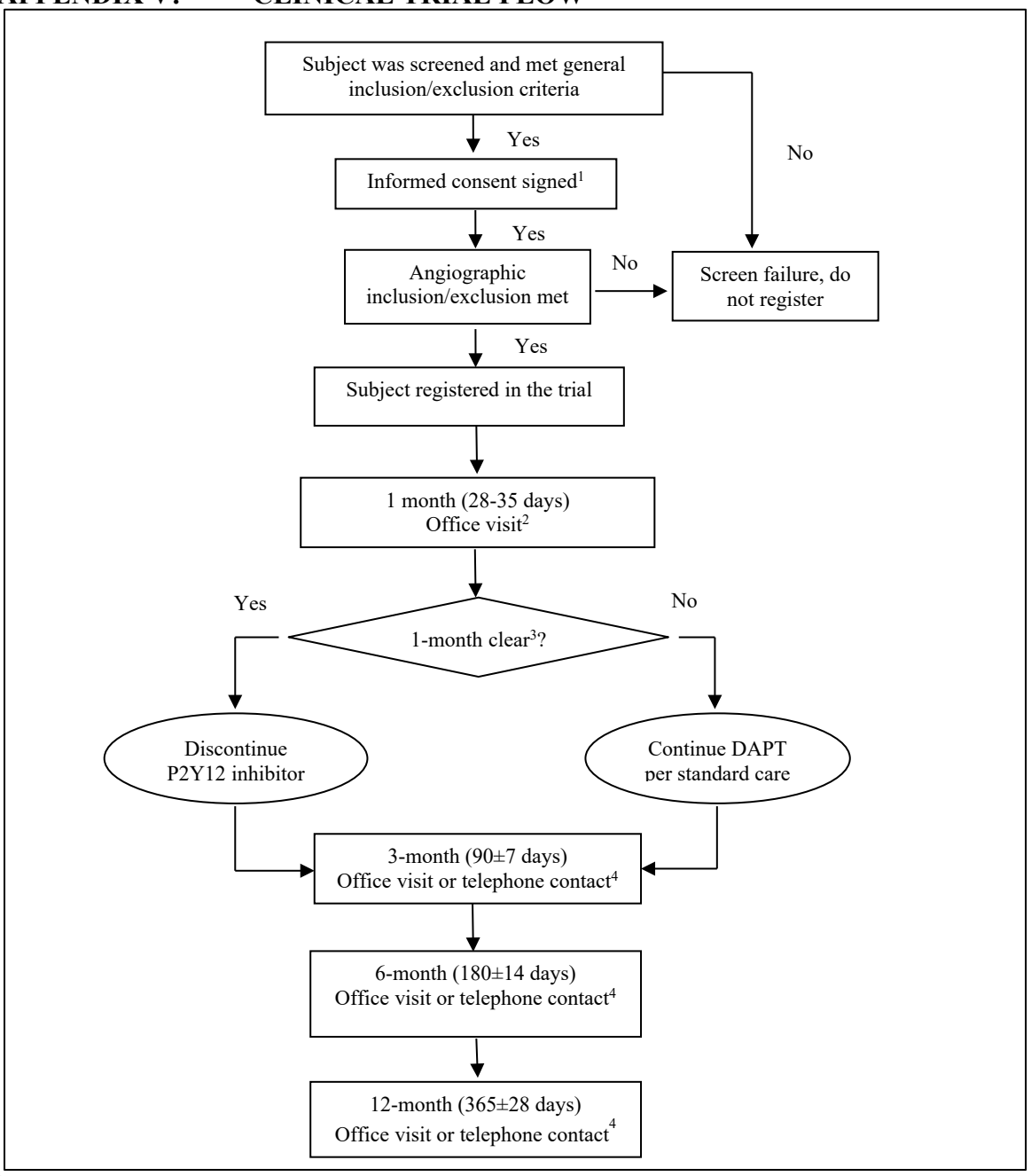
APPENDIX IV: SCHEDULE OF EVENTS

PROCEDURE/TEST	Baseline	Pre-Procedure (within 24 hours)	Procedure	Post-Procedure	1 month (28-35d) Office visit[3]	3 month (90 ±7d) Office visit or phone contact[4]	6 month (180 ± 14d) Office visit or phone contact[4]	12 month (365 ± 28d) Office visit or phone contact[4]	Unscheduled visits
Subject Medical/Clinical History (Age, Sex, Risk Factors, Cardiac Status, Cardiac History)	✓								
Subject Informed Consent (Must be obtained prior to any trial related testing or procedures)[1]	✓								
General Inclusion/Exclusion Criteria	✓								
Angiographic Inclusion/Exclusion Criteria			✓						
Coronary Angiogram			✓						
Stent and Procedure Information			✓						
Antiplatelet Medications Loading Dose		✓[5]	✓[5]	✓[5]					
P2Y12 Inhibitor Discontinuation Eligibility Assessment					✓				
Post-procedure Antiplatelet Medications[2]				✓	✓	✓	✓	✓	✓
Adverse Events			✓	✓	✓	✓	✓	✓	✓

[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.
[2] Subject who are "1-month clear" will discontinue P2Y12 inhibitor as early as 28 days, 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.
[3] A formal office visit is required at 1-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 1-month.
[4] Office visit is strongly recommended whenever possible.
[5] It is recommended that the antiplatelet medication loading dose be given before the procedure (within 24 hours prior to procedure), at time of procedure, or post-procedure (recommended to be within 1 hour post-procedure).

[redacted]

APPENDIX V: CLINICAL TRIAL 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.
[2] A formal office visit is required at 1-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 1-month.
[3] "1-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 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-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

[redacted]

APPENDIX VI: MONITORING PLAN

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

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]

[redacted]

[redacted]