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PROTOCOL 06-374
XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) USA Post-Approval Study

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PROTOCOL SUMMARY

Trial Name and Number	XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) USA Post-Approval Study: 06-374
Objectives	<ul style="list-style-type: none"> • Evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V Everolimus Eluting Coronary Stent System (EECSS) during commercial use by various physicians with a range of coronary stenting experience • Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications • Determine clinical device and procedural success during commercial use • Evaluate patient health status (symptoms, physical function, and quality of life) by the Seattle Angina Questionnaire
Study Design	This prospective, open-label, multi-center, observational, single-arm registry is designed to evaluate XIENCE V EECSS continued safety and efficacy during commercial use in real world settings.
Patient Enrollment	Approximately 5000 patients consecutively enrolled at up to 275 sites in the United States of America
Patient Follow-Up	Clinical follow-up will occur at 14, 30, 180 days and 1, 2, 3, 4, and 5 years. Investigator or designee may conduct follow-up as telephone contacts or office visits.
Primary Endpoint	Academic Research Consortium (ARC) defined stent thrombosis at 1 year
Secondary Endpoints	<ul style="list-style-type: none"> • Stent thrombosis at 24 hours, 30, 180 days and at 2, 3, 4 and 5 years • Composite rate of death, myocardial infarction (MI), and revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]) at 30, 180 days and at 1, 2, 3, 4 and 5 years • Composite rate of cardiac death, MI attributed to the target vessel, and target lesion revascularization (TLR) at 30, 180 days and at 1, 2, 3, 4 and 5 years • Death (cardiac death, vascular death, non-cardiovascular death) at 30, 180, days and at 1, 2, 3, 4 and 5 years • MI (both Q-wave and non Q-wave) at 30, 180 days and at 1, 2, 3, 4 and 5 years • Revascularization (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years • Target vessel revascularization (both PCI and CABG) (TVR) at 30, 180

	<p>days and at 1, 2, 3, 4 and 5 years</p> <ul style="list-style-type: none"> • TLR (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years • Compliance and therapy interruptions with prescribed adjunctive antiplatelet therapy at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years • Major bleeding complications at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years • Clinical device and procedural success • Patient health status (symptoms, physical function, and quality of life) at baseline, 180 days, and 1 year as assessed by the Seattle Angina Questionnaire
Analytical Population	Patients who received only XIENCE V EECSS during the index procedure.
Safety Monitoring	All serious adverse events will be reviewed by an independent data safety monitoring board to ensure public safety throughout the 5-year follow-up. An independent clinical events committee will review and adjudicate according to ARC definitions for the following: death, MI, revascularization, and stent thrombosis. Major bleeding complications will also be adjudicated.
Study Blinding	This study is not blinded.
Treatment Strategy	The treatment strategy will be determined by the investigator. It is recommended that each enrolling investigator review the <i>XIENCE V Everolimus Eluting Coronary Stent System Instructions for Use</i> and assess the contraindications, warnings and precaution sections with respect to risks and benefits for treating potential patients.
Key Inclusion Criteria	The patient agrees to participate in this study by signing the Institutional Review Board approved informed consent form.
Key Exclusion Criteria	The inability to obtain an informed consent.

1 INTRODUCTION

Long term surveillance studies using a drug eluting stent (DES) may help elucidate mechanisms responsible for death, myocardial infarction, and late stent thrombosis risks not observed during controlled pre-market trials.¹ This study will evaluate XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) performance in the “real world” when used by a broad group of physicians at a variety of health care facilities.

Consequently, this protocol will include all consecutively enrolled patients in the United States of America (USA) who consent to participate and receive the XIENCE V EECSS, which is expected to represent the range of clinical use during commercialization.

Adjunctive anti-platelet therapy is a critical factor in optimizing long term DES safety.^{2,3} Despite established guidelines that recommend 6-12 months dual antiplatelet therapy, patients with DES implants frequently stop taking their medication early. Consequently, XIENCE V EECSS USA Post-Approval Study (XIENCE V USA) follow-up will document patient adherence and persistence with adjunctive antiplatelet drug therapy at several time points throughout the study.

2 BACKGROUND INFORMATION

2.1 Coronary Stent History

Coronary stents were introduced in 1987 as a major advance over balloon angioplasty alone for treating atherosclerosis derived coronary artery disease. Coronary stents reduced angiographic and clinical restenosis rates in de novo lesions compared to percutaneous transluminal coronary angioplasty (PTCA) alone and decreased emergency coronary artery bypass graft (CABG) surgery. However, in-stent restenosis resulting in repeat revascularization remained a challenge.^{4,5} In an effort to address the restenosis problem, stents coated with various drug doses and formulations have been developed to reduce neointimal proliferation at the lesion site.⁶⁻⁹

2.2 Drug Eluting Stent Approval

In the United States, CYPHER® Sirolimus-Eluting Coronary Stent System approved April 2003, and TAXUS® EXPRESS²™ Paclitaxel Eluting Coronary Stent System (TAXUS PECSS), approved March 2004 were shown to have preserved safety and improved efficacy when compared to their uncoated bare metal platforms in treating de novo native coronary artery lesions. Conformité Européene Mark approval for the XIENCE V EECSS was received on January 30, 2006 allowing it to be marketed throughout the European Union; it is currently approved in 24 regulated countries and commercially available in over 40 others.

SPIRIT III, a pivotal clinical trial conducted in the USA and Japan, was designed to compare XIENCE V EECSS performance to the TAXUS PECSS. The SPIRIT III USA randomized clinical trial indicates that XIENCE V EECSS efficacy is statistically non-

inferior to the TAXUS PECSS in single and multiple de novo native coronary artery lesions.¹⁰ Moreover, the primary endpoint was met with an in-segment late loss of 0.14 ± 0.41 mm for the XIENCE V EECSS arm and 0.28 ± 0.48 mm for the TAXUS PECSS arm at 240 days (non-inferiority $p < 0.0001$, $\Delta = 0.195$ mm).

Additionally, a pre-specified superiority analysis of the primary endpoint was performed using a two-sided t-test ($\alpha = 0.05$). The analysis indicates XIENCE V EECSS superiority over TAXUS PECSS for the primary endpoint of in-segment late loss at 240 days ($p = 0.0037$). The major secondary endpoint was also met with an ischemia-driven target vessel failure rate of 7.2% (47/657) for the XIENCE V EECSS arm and 9.0% (29/321) for the TAXUS PECSS arm (non-inferiority $p < 0.0001$). Please refer to the *XIENCE V Everolimus Eluting Coronary Stent System Instructions for Use (IFU)* for clinical results from XIENCE V EECSS trials.

2.3 Late Stent Thrombosis and Antiplatelet Therapy

Following the European Society of Cardiology Scientific Congress (September 2006) and the Transcatheter Cardiovascular Therapeutics meeting (October 2006), attention has focused on the relationship between late stent thrombosis and drug eluting stents. A subsequent Food and Drug Administration (FDA) public meeting of the Circulatory System Devices Advisory Panel (December 2006) met to review data presented from multiple randomized control trials and registries in order to determine the extent of this relationship and whether measures can be taken to reduce late stent thrombosis risk following stent implantation.

Data from the ARRIVE-1 registry evaluated patients who received a paclitaxel eluting stent. Twelve month follow-up results for patients that had discontinued dual antiplatelet therapy at 6 months indicated an overall 4.7% stent thrombosis rate per stented vessel (17/362), a rate more than twice that of the 1.7% stent thrombosis rate for patients who continued therapy through to 6 and 12 months.¹¹

In a meta-analysis conducted on 14 clinical trials that randomized 6675 patients to paclitaxel or sirolimus eluting stents versus bare metal stents, the late stent thrombosis rate in the sirolimus group was 0.35% (3.5/1000) compared to 0.49% (4.9/1000) with bare metal stents and 0.63% (6.3/1000) in the paclitaxel group compared to 0.11% (1.1/1000) with bare metal stenting.¹² In these studies, antiplatelet therapy use was inconsistent, varying widely from 2-12 months duration in sirolimus trials and 6 months for paclitaxel trials. Following the FDA panel meeting, a Science Advisory has been released recommending patients who are not at high bleeding risk to remain on dual antiplatelet therapy for up to 12 months.²

The PREMIER registry results also examined compliance to recommended antiplatelet therapy.³ Patients with acute myocardial infarction (AMI) that stopped antiplatelet therapy by 30 days (13.6%, 68/500) post-procedure had higher mortality (7.5% versus 0.7%, $p < 0.0001$) and re-hospitalization (23% versus 14%, $p = 0.08$) rates during the next 11 months than those who continued therapy. Almost 1 in 7 of these AMI patients terminated dual antiplatelet therapy by 30 days. These patients tended to be older, were less likely to have completed high school or be married, and were less likely to have

received discharge instructions and a cardiac rehabilitation referral. These patients also had more preexisting cardiovascular disease or anemia at presentation than those adhering to antithrombotic therapy.

Taken together, these studies emphasize the importance of encouraging patients to take their prescribed antiplatelet medication and make it essential to identify non-compliance risk factors to develop preventative strategies for reducing late stent thrombosis risk in patients receiving drug eluting stents. Consequently, XIENCE V USA will extensively monitor and collect data on dual antiplatelet therapy compliance.

2.4 Quality of Life and the Seattle Angina Questionnaire

In clinical trials, a patient reported quality of life outcome instrument can be used to measure the impact of an intervention on several aspects of patient health status. There is a desire to know the patient perspective about treatment effectiveness since improvements in clinical measures may not correlate with how the patient feels or functions. In addition, obtaining the patient's perspective may provide valuable information that can be misrepresented or lost through a clinician centered evaluation.

Recently, data from the "Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation" (COURAGE) trial suggest that stenting has no additional benefits over drug therapy in improving life threatening outcomes in a selective study population with coronary artery disease.¹³ However, quality of life data obtained during this trial using the Seattle Angina Questionnaire indicate the proportion of angina-free patients was significantly higher at 1 and 3 years in the percutaneous coronary intervention (PCI) group with lower anti-angina medication use. This important patient-centered benefit may play a critical role in determining reimbursement preferences for stenting vs. drug therapy in populations where these 2 treatments deliver clinically comparable outcomes. The validated, unmodified Seattle Angina Questionnaire will be administered as part of XIENCE V USA in order to determine treatment effects on patient assessed outcomes using the patient as his own control.¹⁴

2.5 Description of the XIENCE V EECSS

The XIENCE V EECSS is composed of 2 regulated components: a device (MULTI-LINK VISION® and MINI VISION® Coronary Stent System) and a drug (a formulation of everolimus contained in a polymer coating). Refer to the IFU for descriptions, indications for use, contraindications, system preparation, precautions, and warnings.

This protocol is designated for both over-the-wire and rapid exchange delivery systems. For this document, XIENCE V EECSS will refer to both delivery systems.

3 STUDY OBJECTIVES

Study objectives consist of the following:

- Evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V EECSS during commercial use by various physicians with a range of coronary stenting experiences;
- Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications;
- Determine clinical device and procedural success during commercial use (refer to section 17.1 Appendix I Definitions);
- Evaluate patient health status (symptoms, physical function, and quality of life) by the Seattle Angina Questionnaire.

4 STUDY DESIGN

4.1 Study Design

XIENCE V USA is a prospective, open-label, multi-center, observational, single-arm registry to monitor XIENCE V EECSS continued safety and efficacy during commercial use in real world settings.

4.2 Patient Enrollment

Approximately 5000 patients will be consecutively enrolled in this study at up to 275 sites across the USA. Data from all study sites will be pooled for analyses.

4.3 Patient Follow-up

Clinical follow-up will occur at 14, 30, 180 days and 1, 2, 3, 4, and 5 years. The investigator or designee may conduct follow-up as telephone contacts or office visits.

4.4 Early Study Termination

No statistical rule for early trial termination is defined. However, Abbott Cardiovascular Systems Incorporated, a subsidiary of Abbott Vascular (Abbott Vascular) may discontinue the study at any stage with written notice to the investigator. Possible reasons for early termination may include a plateau or decrease in stent thrombosis rates or unanticipated adverse device effects that may present unreasonable patient risk.

The Executive Committee makes a final decision for early study termination based on Data Safety Monitoring Board (DSMB) recommendations (refer to section 8.5 Safety Monitoring).

If a trial is terminated early, Abbott Vascular will provide a written statement describing why premature termination will occur, and notify the Institutional Review Board (IRB) and the regulatory authority (if applicable). All applicable clinical study documents will be subject to the same retention policy as detailed in section 12 Data Handling and Record Keeping.

4.5 Measures Taken to Avoid/Minimize Bias

In order to minimize bias in assessing clinical events, an independent Clinical Events Committee (CEC) (section 8.6.1 Clinical Events Committee) and DSMB (section 8.5.1 Data Safety Monitoring Board) will be established.

4.6 Treatment Strategy

The treatment strategy will be determined by the investigator. It is recommended that each enrolling investigator review the most recent IFU to assess contraindications, warnings, and precautions for treating potential patients.

5 ENDPOINTS

5.1 Primary Endpoint

Academic Research Consortium (ARC) defined stent thrombosis at 1 year

5.2 Secondary Endpoints

- Stent thrombosis at 24 hours, 30, 180 days and at 2, 3, 4 and 5 years
- Composite rate of death, myocardial infarction (MI), and revascularization ([PCI] and [CABG]) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Composite rate of cardiac death, MI attributed to the target vessel, and target lesion revascularization (TLR) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Death (cardiac death, vascular death, non-cardiovascular death) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- MI (both Q-wave and non Q-wave) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Revascularization (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Target vessel revascularization (both PCI and CABG) (TVR) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- TLR (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Compliance and therapy interruptions with prescribed adjunctive antiplatelet therapy at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years
- Major bleeding complications at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years

- Clinical device and procedural success
- Patient health status (symptoms, physical function, and quality of life) at baseline, 180 days, and 1 year assessed by the Seattle Angina Questionnaire

6 PATIENT SELECTION AND WITHDRAWAL

6.1 Patient Population

Approximately 5000 patients derived from the USA interventional cardiology population will be enrolled in this study. It is recommended that each enrolling investigator review the most recent IFU and assess the contraindications, warnings, and precaution sections for treating potential patients. In addition to patients who meet criteria outlined in the IFU, the study will likely obtain data for lesion settings not previously studied.

6.2 Patient Screening

All patients admitted for PCI should be invited to participate in the study. Patients will be entered into the electronic Case Report Form (eCRF) screening log only if informed consent is obtained and XIENCE V EECSS stent(s) is (are) implanted into the subject's coronary vasculature during the index procedure.

6.3 Eligibility Criteria

6.3.1 General Inclusion Criteria

The patient agrees to participate in this study by signing the IRB approved informed consent form. Alternatively, the patient's legally authorized representative agrees to the patient's participation in this study and signs the informed consent form.

6.3.2 General Exclusion Criteria

The inability to obtain an informed consent is an exclusion criterion.

6.3.3 Angiographic Inclusion Criteria

There are no angiographic inclusion criteria for this study.

6.3.4 Angiographic Exclusion Criteria

There are no angiographic exclusion criteria for this study.

6.4 Point of Enrollment

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent and only XIENCE V EECSS stent(s) is (are) received during the index procedure. The study will sequentially enroll all consenting patients who have met these criteria.

6.5 Patient Discontinuation

Once enrolled, each patient should remain in the study until the required follow-up period is complete. However, the patient has the right to withdraw from the study at any time without penalty or loss of benefit. Data obtained to the last follow-up will be used for the analysis. The following events will result in terminating the patient's follow-up:

- Patient death
- Patient voluntary withdrawal
- Patient withdrawn by investigator as clinically indicated
- Patient lost to follow-up (unofficial withdrawal)
- Study is terminated according to section 4.4 Early Study Termination

An eCRF must be completed for both terminated patients and patients who complete the entire 5-year follow-up. Abbott Vascular must be notified of the reason for patient discontinuation. The site will provide this information on the eCRF. Investigators must also report this information to the local IRB as defined by their institution's procedure.

6.5.1 Lost to Follow-up

Patients that do not complete the scheduled follow-up visits and have not officially withdrawn from the study are considered lost to follow-up; this term does not apply to missed visits. Site personnel should make considerable effort to locate and communicate with the patient using all available methods (eg, telephone, emails, and postcards). The following contact procedure is recommended at each time point:

- A minimum of 2 telephone calls on different days over the specified follow-up windows should be recorded in the source documentation including date, time, and site personnel initials for staff attempting to contact the patient.
- If these attempts are unsuccessful, a certified letter should be sent to the patient.
- If the patient misses 2 consecutive scheduled contact time points and the above mentioned attempts at communicating with the patient are unsuccessful, the patient will be considered lost to follow-up.

7 TREATMENT OF PATIENTS

The schedule of events for this trial is located in section 17.4 Schedule of Events. The treatment strategy will be determined by the investigator. It is recommended that each enrolling investigator review the most recently updated IFU and assess the contraindications, warnings, and precaution sections for treating potential patients.

It is recommended that enrolling investigators follow these guidelines when applicable:

- American College of Cardiology (ACC)/American Heart Association (AHA) /Society for Cardiovascular Angiography and Interventions (SCAI) 2005 Guideline Update for Percutaneous Coronary Intervention¹⁵

- AHA/ACC Secondary Prevention Guidelines¹⁶
- Third Report National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III Guidelines)¹⁷
- The Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹⁸

7.1 Antiplatelet Medication

Although antithrombotic management is ultimately determined by investigators, enrolled patients will be encouraged to receive adjunctive antiplatelet therapy consisting of an indefinite duration of aspirin, along with 6 months of clopidogrel. Clopidogrel will be extended to 12 months in patients who are not at high bleeding risk as recommended by ACC/AHA/SCAI and others.² The following information is stated in the IFU:

It is very important that patients comply with the post-procedural antiplatelet recommendations. Prematurely discontinuing prescribed antiplatelet medication may result in higher stent thrombosis, myocardial infarction or death risk. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, procedural risks and benefits should be weighed against the risk associated with prematurely discontinuing antiplatelet therapy.

Patients who prematurely discontinue antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, their antiplatelet therapy should be restarted as soon as possible per treating physician discretion.

7.2 Baseline

The baseline time point consists of clinical visits that occur up to 4 weeks prior to the index procedure. Patients will be prepared according to the healthcare facility's standard care for interventional cardiology patients.

If available, the following data should be collected at baseline:

- Demographics including age, gender, and race
- Cardiac history including Canadian Cardiovascular Society and Braunwald classifications of angina, diabetes mellitus, hypertension, dyslipidemia, previous CABG and PCI, renal insufficiency, and anemia
- Socioeconomic status including marital status, education, employment, and healthcare access
- Physical measurements including weight, height, waist and hip circumferences, and blood pressure

- Other risk factors including tobacco use, family history of coronary artery disease, and stroke
- Patient health status (symptoms, physical function, and quality of life) using the Seattle Angina Questionnaire
- Eligibility criteria similar to XIENCE V EECSS pivotal trials (Appendix V XIENCE V EECSS Pivotal Study Eligibility Criteria)
- Chronic concomitant medication
- Baseline Angiogram

Any of the above data that is not collected during the baseline time window may be obtained post-procedure and will still be considered baseline data; refer to section 17.4 Schedule of Events for specific time periods.

If available, the following baseline laboratory assessments should be collected:

- White blood cell count (WBC), platelet cell count, hemoglobin, and hematocrit
- Lipid profile (LDL, HDL, triglycerides, and total cholesterol)
- Apolipoprotein A1 (APOAI) and B (APOB)
- Serum insulin, serum glucose, and hemoglobin A_{1c} (HbA_{1c})
- Serum creatinine

If available, the following pre-procedural laboratory assessments should be collected:

- Pre-procedural creatine kinase (CK), creatine kinase myocardial band isoenzyme (CK-MB), and/or troponin (the most recent assessment)
- Electrocardiogram (ECG)

7.3 Procedure

Patients will receive appropriate therapies (eg, anticoagulation) according to standard healthcare facility practice. The XIENCE V EECSS will be inspected, prepared, and implanted according to the IFU. If available during the procedure, the following data should be collected:

- Antiplatelet loading dose
- Stent use attributes (eg, size, diameter, overlapping, number of stents)
- Product performance
- Lesion characteristics (ACC/AHA Classification Scheme of Coronary Lesions)
- Clinical events that occur during the procedure including death, MI, revascularization, and stent thrombosis. Adverse event (AE) data with related laboratory test results, ECG, and subsequent repeat coronary angiography results.
- CK, CK-MB, and/or troponin (collect immediately post-procedure)

- ECG (collect immediately post-procedure)
- Discharge instructions
- Procedural complications (Abrupt closure, dissection, no-reflow, etc)

The Seattle Angina Questionnaire may be administered to the patient anytime prior to discharge no later than 14 days post procedure if it is not completed at baseline.

8 SAFETY and EFFICACY ASSESSMENT

8.1 Clinical Follow-up

Clinical follow-up will occur as a telephone contact or office visit at the following time points:

Follow-up time point	± days
14 days*	7
30 days	7
180 days	14
1 year	42
2 years	42
3 years	42
4 years	42
5 years	42

*This time point applies only to antiplatelet therapy compliance, bleeding complications and concomitant medications.

If a patient completes a clinic visit independent of this protocol and outside the protocol-required follow-up time points, this information will be obtained from the patient's source documents. All efforts must be made to obtain follow-up information on patients who have received procedures or have been treated for serious adverse events (SAE) in a non-study-related health care facility.

If available, the following data should be collected at the specified time points:

- Clinical events including death, MI, revascularization, and stent thrombosis at 30, 180 days and 1, 2, 3, 4, and 5 years. Also, AE related data including laboratory test results, ECG, and subsequent repeat coronary angiography results
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications at 14, 30, 180 days and 1, 2, 3, 4, and 5 years
- Patient health status (symptoms, physical function, and quality of life) using the Seattle Angina Questionnaire at 180 days and 1 year
- Chronic concomitant medication at 14, 30, 180 days and 1, 2, 3, 4, and 5 years

8.1.1 Additional Event-Driven Visits

Additional event-driven visits may occur as clinically warranted. If available, the following data should be collected at these visits:

- Clinical events including death, MI, revascularization, and stent thrombosis. Also, AE related data including laboratory test results, ECG, details, and subsequent coronary angiography results
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications
- Chronic concomitant medication

8.2 Adverse Events

During each clinical follow-up, the investigator or designee will determine AE occurrences. An AE is defined as any untoward medical occurrence in a patient or clinical investigation when the patient was administered a study device which does not necessarily have a causal relationship with this treatment.

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

8.2.1 Serious Adverse Event

An SAE is fatal or leads to a serious deterioration in health resulting in the following:

- A life-threatening situation
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.2 Serious Injury

A serious injury is defined by the following:

- Life-threatening injuries/illnesses

- Injuries/illnesses resulting in permanent impairment of a body function or permanent damage to a body structure
- Injuries/illnesses necessitating medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Here, “permanent” is defined as irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Collection of AEs begins when procedure starts. Pre-existing conditions are not reported as AEs unless there has been a worsening in severity or frequency which cannot be attributed to the disease’s natural history or progression. Event description, date of onset, duration, treatment, outcome, and relationship to device will be collected on the AE eCRF.

There are no experimental procedures being conducted in this post-approval study. Only approved products are being used according to the IFU and current clinical practice standards.

It is recommended that effective contraception should be initiated before implanting a XIENCE V EECSS stent and continued for one year post-implantation. The XIENCE V EECSS stent should be used in pregnant women only if potential benefits justify potential risks. XIENCE V EECSS safety has not been evaluated in males intending to father children.

8.3 Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADE) are any serious adverse effects on health, safety or any life-threatening problem or death caused by, or associated with the investigational study device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the IFU.

When an AE meets the definition of a UADE or that relationship is unknown, the investigator will report the event to Abbott Vascular within 24 hours but no later than 10 working days after the investigator first learns of the effect and reports to the reviewing IRB as required.

8.4 Medical Device Reporting

8.4.1 Manufacturer Reporting Requirements

The XIENCE V EECSS device is commercially available and subject to FDA Medical Device Reporting (MDR) regulations. These regulations require manufacturers who receive complaints of device malfunctions, serious injuries or deaths associated with medical devices to notify FDA of the incident.

Consequently, Abbott Vascular will comply with the MDR requirements for devices used in this study through the information gathered on the eCRFs and source documents from the site. The collective information required on form 3500A and Abbott Vascular routing procedures are designed to comply with time sensitive reporting requirements. Abbott Vascular will submit MDR reports according to FDA 21 CFR 803.50 through 803.58.

8.4.2 Clinical Site Reporting Requirements

Death and serious injury reporting is captured on the product performance eCRF provided by Abbott Vascular according to 21 CFR 803.30 and 803.32 as follows:

- The User Facility must report when the XIENCE V EECSS device has or may have caused or contributed to a patient death within 10 days of becoming aware of the incident. This User Facility report must be submitted to Abbott Vascular.
- The User Facility must report when the XIENCE V EECSS device has or may have caused or contributed to a patient serious injury within 10 days of becoming aware of the incident. This User Facility report must be submitted to Abbott Vascular.

The User Facility reports shall include the following information:

- Patient information
- AE description or product problem
- Outcomes attributed to the AE, such as death or serious injury that includes any of the following:
 - a) A life threatening injury or illness
 - b) A disability resulting in permanent impairment of a body function or permanent damage to a body structure
 - c) An injury or illness that requires intervention to prevent permanent impairment a body structure or a body function
- Device information
- User facility and initial reporter information

Throughout the study, Abbott Vascular will report to FDA on death, myocardial infarction, revascularization, stent thrombosis, major bleeding complication, and all unanticipated device-related events in the interim post-approval study status reports. The interim post-approval study status report will normally be submitted every 6 months for the first 2 years of the study and annually thereafter until the final report has been submitted according to Guidance for Industry and FDA staff: Procedures for Handling Post-approval Studies Imposed by PMA Order.

8.5 Safety Monitoring

8.5.1 Data Safety Monitoring Board

The DSMB is composed of general and interventional cardiologists, and a biostatistician. The board members are independent and will not be participating in the trial and will not be affiliated with Abbott Vascular, investigators or investigational sites. The DSMB is responsible for making recommendations regarding any safety or compliance issues throughout the course of the study and may recommend to the Executive Committee to modify or stop the study. However, all final decisions regarding study modifications rest with the Executive Committee.

All cumulative safety data will be reported to the DSMB and reviewed on an ongoing basis throughout enrollment and follow-up periods to ensure patient safety. Every effort will be made to allow the DSMB to conduct an unbiased review of patient safety information. All DSMB reports will be made available to the FDA upon request but will otherwise remain strictly confidential.

8.6 Event Adjudication

8.6.1 Clinical Events Committee

The CEC is composed of independent interventional and/or non-interventional cardiologists who are not participating in this study and will not be affiliated with Abbott Vascular. The CEC will review and adjudicate according to ARC definitions for the following: death, MI, revascularization, stent thrombosis (refer to section 17.1 Appendix I Definitions). In addition, CEC will also review and adjudicate major bleeding complications and suspected UADEs.

9 STATISTICAL DESIGN AND ANALYSIS

9.1 Statistical Overview

The purpose of this study is to evaluate XIENCE V EECSS continued safety and efficacy during commercial use in real world settings.

9.2 Analysis Populations

The analytical population will consist of patients who received only the XIENCE V EECSS device during the index procedure. Other sub-populations will be detailed in the statistical analysis plan.

9.3 Sample Size Calculations and Assumptions

The 5000 patient sample size for this study was derived using the anticipated stent thrombosis rate and the precision of this estimate based on the following:

- A 1-year cumulative ARC defined stent thrombosis rate of 1.7% derived from past XIENCE V EECSS trials,

- A standard error of 0.18% for the stent thrombosis rate estimate
- A 2% dropout rate for the overall population at 1-year follow-up (based on ARRIVE study result data)

The estimated stent thrombosis rate and standard error correspond to an approximate 95% confidence interval from 1.35% to 2.05%.

9.4 Statistical Analyses

9.4.1 Primary Analysis

Stent thrombosis rates and confidence intervals will be summarized at 24 hours, 30, 180 days and 1, 2, 3, 4 and 5 years.

9.4.2 Secondary Analysis

Secondary endpoints will be summarized for the analytical population and certain sub-populations. Two-sided 95% confidence intervals will be calculated for event rates. Descriptive analyses will be provided for patient demographics, clinical device/procedural success, antiplatelet therapy compliance, bleeding complications, medical histories, and co-morbidities. Logistic regression analyses may be used to screen a wide range of parameters for their association with some endpoints. Health status will be assessed by including predetermined categories from the Seattle Angina Questionnaire. Each patient will serve as their own control. Correlation analyses will be conducted for several parameters including, but not limited to, adjunctive dual antiplatelet therapy use, bleeding complications, and late stent thrombosis incidence.

9.4.3 Criteria for Efficacy Related Early Trial Termination

There are no criteria to terminate this trial for efficacy.

9.4.4 Procedures to Account for Missing Data

A propensity score based method may be used to impute missing data.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

Consenting patients are agreeing to allow Abbott Vascular or designee access and copying rights to pertinent information in their medical records relevant to study participation. As part of the informed consent, the investigator or designee will obtain permission for regulatory authorities to review any records identifying patients in this study. Abbott Vascular will not otherwise release any personal information (refer to section 13.3 Confidentiality).

11 QUALITY CONTROL AND ASSURANCE

11.1 Clinical Site and Investigator Selection

Abbott Vascular will select qualified investigators with varying interventional cardiology experience at health care facilities with adequate resources to participate in this study. Sites will be selected using combined current assessments of site and investigator qualifications.

11.2 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well being of the patient. In the event of any deviation from the protocol, a Protocol Deviation Case Report Form will be completed. The occurrence of protocol deviations will be monitored by Abbott Vascular for evaluation of Investigator compliance to the protocol, Good Clinical Practice (GCP), and regulatory requirements. The Investigator will inform the IRB of all protocol deviations according to requirements of each reviewing IRB.

The protocol deviation for this protocol consists of, but not limited to, the following:

- Failure to obtain patient's informed consent prior to any study-related activities and the index procedure
- Stent(s) other than XIENCE V implanted during the index procedure
- Failure to conduct protocol required clinical follow-ups and within time windows
- Failure to report serious adverse events according to protocol requirements

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required if necessary. Continued protocol deviations despite re-education of study site personnel or persistent protocol deviations may result in termination of the site's study participation. Patients already enrolled at these sites will continue to be followed per protocol guidelines.

11.3 Training

Abbott Vascular will be responsible for providing training to the investigator and appropriate clinical site personnel. It is recommended that investigators review the IFU.

11.3.1 Monitor Training

Abbott Vascular and/or designated monitors will be trained appropriately to monitor study progress including but not limited to the protocol and eCRFs.

11.4 Good Clinical Practice Compliance

The trial will be conducted in compliance with the protocol, Good Clinical Practices and applicable regulatory requirements.

11.5 Study Monitoring

11.5.1 Site Monitoring

A study specific monitoring plan will be conducted to ensure protocol compliance and applicable regulatory requirements.

11.5.2 Compliance Assessments

Abbott Vascular or designee may conduct periodic compliance assessments at various study sites. Abbott Vascular or designee may request access to all trial records including source documentation for inspection and duplication during a compliance assessment. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

11.5.3 Regulatory Agency Inspection

In the event that an investigator is contacted by a regulatory agency regarding this trial, the investigator will notify Abbott Vascular immediately. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The investigator must provide Abbott Vascular or designee with copies of all correspondence that may affect review of the current trial (eg, Form FDA 483, Inspectional Observations, and Warning Letters). Abbott Vascular may provide needed assistance in responding to regulatory audits.

11.6 Committees

11.6.1 Executive Committee

The Executive Committee may be composed of Principal Investigators, the study Chairperson, and Abbott Vascular's Vice President of Regulatory Affairs/Clinical Research. The Chairperson of the core laboratories and Abbott Vascular's Director(s) of Clinical Research, Managers/Fellows of Clinical Research, and Project Managers may also participate in committee meetings if appropriate. This committee will oversee general aspects of the study including final protocol review, ongoing general data collection monitoring, and review of implementation and/or operational issues that may arise and warrant a protocol amendment or other corrective action. The Executive Committee will also approve policy regarding presentations and/or publications.

11.6.2 Operations Committee

The Operations Committee is an Abbott Vascular designated team composed of clinical research representatives that will be responsible for daily administrative trial management. This committee will monitor patient enrollment, clinical site progress, and protocol compliance. The committee will also provide assistance to sites with trial

management issues, including compliance with specific record keeping and reporting requirements.

11.6.3 Publication Committee

The Publication Committee is composed of representatives from Abbott Vascular Clinical Research, investigators, and other personnel as determined by the committee Chairperson and approved by the Executive Committee. This team will oversee presentation and/or publication aspects of the study. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from study generated data. The committee will also review all external requests for accessing study related data and strategies aligning with Abbott Vascular presentation and publication team expectations. The committee will also follow Abbott Vascular applicable policies and standard operating procedures.

12 DATA HANDLING AND RECORDKEEPING

For the study duration, the investigator will maintain complete and accurate documentation including but not limited to the following: medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, device serial numbers for monitoring malfunctions, correspondence with the IRB and study monitor/Abbott Vascular, AE reports, and information regarding patient discontinuation or study completion.

12.1 Source Documentation

The following materials should be included in the patient record:

- Patient medical history/physical condition prior to study involvement
- Dated and signed notes on the day of entry into the study referencing Abbott Vascular, protocol number, site and patient ID number, and a statement that confirming informed consent
- Dated and signed notes from each patient's visit (for specific results of procedures and exams)
- AEs reported and their outcome including supporting documents
- Patient's condition upon study completion or withdrawal

12.2 Case Report Form Completion

Accurate primary data collection will be performed by research coordinators at each clinical site trained on the protocol and eCRF completion. Abbott Vascular or designee will provide clinical monitoring to include eCRF review and parity checks with the source documentation, including operator worksheets retained with eCRF documentation and health care facility charts.

12.3 Record Retention

The Primary Investigator should maintain all records pertaining to this study for 2 full years following study completion or as otherwise instructed by Abbott Vascular. Abbott Vascular will maintain copies of correspondence, data, adverse device effects and other relevant clinical study records.

13 ETHICAL CONSIDERATIONS

13.1 Institutional Review Board Review

Institutional Review Board approval for the protocol and informed consent form will be obtained by the investigator prior to study participation. The approval letter must be signed by the IRB Chairperson or authorized representative prior to beginning this study and a copy must be provided to Abbott Vascular. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB, Abbott Vascular and/or the regulatory agencies. Additionally, the Primary Investigator or representative will provide an IRB membership list or assurance number to Abbott Vascular.

According to IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

13.2 Informed Consent

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. Failure to obtain signed informed consent will render the patient ineligible for the study. All enrolled patients will sign a consent form that has been approved by both Abbott Vascular and the IRB. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. The consent form or a separate authorization form will include language that satisfies the Health Insurance Portability and Accountability Act of 1996 (45 CFR Parts 160 and 164) and associated regulations.

13.3 Confidentiality

To ensure compliance with the Health Insurance Portability and Accountability Act of 1996, confidentiality of protected health information shall be maintained by all parties involved at all times throughout the clinical trial. All data should be secured against unauthorized access. Study patients will be assigned a unique coded identifier on eCRFs and other study records sent to Abbott Vascular.

13.4 Submitting Reports

Abbott Vascular will submit interim post-approval study reports to FDA every 6 months for the first 2 years of the study and annually thereafter until the final post-approval study report has been submitted. Annual clinical updates will be sent to investigators.

14 PROTOCOL AMENDMENTS

Approved protocol amendments will be provided to investigators by Abbott Vascular prior to implementation. The Primary Investigator will be responsible for notifying the IRB of the protocol amendment with administrative changes or obtaining IRB approval of the protocol amendment with changes in patient care or safety, according to instructions provided by Abbott Vascular with the protocol amendment. Institutional Review Board acknowledgements/approvals must be documented in writing prior to implementing protocol amendments. Copies of this documentation must also be provided to Abbott Vascular.

15 TERMINATION OF STUDY SITE PARTICIPATION

Abbott Vascular reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include the following:

- Unsatisfactory patient enrollment
- Failure to comply with protocol
- Failure to comply with Good Clinical Practice
- Inaccurate and/or incomplete data recording on a recurrent basis

The investigator may also discontinue study participation with suitable written notice to Abbott Vascular.

16 PUBLICATION POLICY

Study derived data are the sole property of Abbott Vascular. Investigators will not use study related data without written consent from Abbott Vascular for any purpose other than study completion or for generating publication material as stated in the study site agreement. The presentation and/or publication of results from a single study site cannot precede presentation and/or publication of multi-center results. Abbott Vascular acknowledges that the Principal Investigators intend to publish a multi-center publication regarding the study results. Proposed presentation and/or publication materials must be received at least 60 days prior to the proposed submission date to be reviewed by Abbott Vascular for compliance with the publication policy stated in study site agreement. Exceptions to this timeline must be approved by the Executive Committee.

17 APPENDICES

17.1 Appendix I Definitions

Abrupt Closure (Acute Closure)

Occurrence of new severely reduced flow Thrombosis In Myocardial Infarction (TIMI) grade 0 or 1 within the target vessel during the index procedure that persists and requires rescue by a non-assigned treatment strategy (including emergency surgery), or results in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment lesion or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote “no reflow” (due to microvascular flow limitation), in which the vessel is patent but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application reversed the closure.

- **Subabrupt Closure**

Abrupt closure that occurs after the index procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

- **Threatened Abrupt Closure**

Grade B dissection and $\geq 50\%$ diameter stenosis or any dissection of grade C or higher.

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

Type A Lesions (High Success, >85%; Low Risk)	
<ul style="list-style-type: none">• Discrete (< 10 mm length)• Concentric• Readily accessible• Nonangulated segment, < 45°• Smooth contour	<ul style="list-style-type: none">• Little or no calcification• Less than totally occlusive• Not ostial in location• No major branch involvement• Absence of thrombus
Type B Lesions* (Moderate Success, 60-85%; Moderate risk)	
<ul style="list-style-type: none">• Tubular (10-20 mm length)• Eccentric• Moderate tortuosity of proximal segment• Moderately angulated segment, > 45°, < 90°• Irregular contour	<ul style="list-style-type: none">• Moderate-to-heavy calcification• Total occlusions < 3 mo old• Ostial in location• Bifurcation lesions requiring double guide wires• Some thrombus present
* Type B1 lesions: One adverse characteristic * Type B2 lesions: \geq two adverse characteristics	
Type C Lesions (Low Success, <60%; High Risk)	
<ul style="list-style-type: none">• Diffuse (> 2 cm length)• Excessive tortuosity of proximal segment• Extremely angulated segments > 90°	<ul style="list-style-type: none">• Total occlusions > 3 mo old• Inability to protect major side branches• Degenerated vein grafts with friable lesions

Anticipated Adverse Event

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or IFU, that is identified or worsens or occurs in frequency that is not considered normal during a clinical trial. *See also:* **Adverse Event (AE), Serious Adverse Event (SAE), Unanticipated Adverse Device Effect (UADE)**

Adverse Device Effect

Any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions For Use or the deployment of the device. It also includes any event that is a result of a user error.

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation when the patient was administered a study product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the study product. *See also:* **Anticipated Adverse Event, Serious Adverse Event (SAE), Unanticipated Adverse Device Effect (UADE)**

AE

Please see Adverse Event

Analytical Population

The analytical population consists of patients who received only XIENCE V EECSS during the index procedure.

Aneurysm

An abnormal expansion or protrusion of a coronary blood vessel resulting from a disease or weakening of the vessel wall (all 3 layers) that exceeds the reference vessel diameter by 1.5 times

Angina

Braunwald Classification of Unstable Angina¹⁹

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

II. Angina at rest, subacute: Patients with 1 or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

III. Angina at rest, acute: Patients with 1 or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society Classification of Stable Angina

I. Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.

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

III. Marked. Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

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

Bifurcation Lesion

A lesion located at both the main vessel and a side branch of that main vessel.

Bleeding/Hemorrhagic Complications

Bleeding will be classified by the Thrombosis in Myocardial Infarction hemorrhage classification and according to the American College of Cardiology National Cardiovascular Data Registry scheme as defined below:

A. Minimal: Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin (Hgb) < 3 g/dL (or, when Hgb is not available, a fall in hematocrit (Hct) of < 9%).*

B. Minor: Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when Hgb is not available, a fall in Hct of 9 to < 15%).*

C. Major: Clinically significant overt signs of hemorrhage and/or intracranial/intraocular bleeding is present and associated with a drop in Hgb of > 5 g/dL (or, when Hgb is not available, an absolute drop in Hct of > 15%).*

*To account for transfusion, Hgb and Hct measurements will be adjusted for any packed red blood cells or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase of 1 g/dL in Hgb or of 3% in Hct. Thus, to calculate the true change in Hgb or Hct if there has been an intervening transfusion between two blood measurements, the following calculations should be performed:

$$\text{Hgb} = [\text{baseline Hgb} - \text{post transfusion Hgb}] + [\text{number of transfused units}]$$
$$\text{Hct} = [\text{baseline Hct} - \text{post transfusion Hct}] + [\text{number of transfused units} \times 3]$$

The following will be classified as “Instrumented” Major Bleeding that is considered to be associated with the catheterization laboratory visit:

1. Major Percutaneous Entry Site

Bleeding occurred at the percutaneous entry site during or after the catheterization laboratory visit until discharge. The bleeding should require a transfusion and/or prolong the health care facility stay, and/or cause a drop in Hgb > 5 g/dL. Bleeding at the percutaneous entry site can be external or a hematoma >10 cm for femoral access or > 2 cm for radial access; or > 5 cm for brachial access.

2. Major Retroperitoneal, Gastrointestinal, and Genital/Urinary

Bleeding occurred during or after the catheterization laboratory visit until discharge. The bleeding either requires surgical intervention (eg, to relieve nerve compression), and/or requires a transfusion and/or prolong the health care facility stay, and/or cause a drop in hemoglobin > 5.0 g/dL.

3. Major Other/Unknown

Bleeding occurred at other or unknown locations during or after the catheterization laboratory visit until discharge. The bleeding should require a transfusion and/or prolong the health care facility stay, and/or cause a drop in Hgb > 5 g/dL.

D. Instrumented: Hemorrhage that occurs as a result of an invasive procedure

E. Spontaneous: Hemorrhage which is not the direct result of an invasive procedure (eg, gums, gastro-intestinal, nose)

See also: Thrombosis in Myocardial Infarction (TIMI) Flow Grade

CABG

Please see **Coronary Artery Bypass Graft Surgery**

Cardiac Death

Please see **Death**

Chronic Concomitant Medication

Chronic concomitant medication refers to the following:

- a) medication that has been prescribed or is over the counter, that has been taken or will continue to be taken regularly for at least a period of 6 months; or
- b) medication that is required to be taken indefinitely by the patient; or

c) medication that has been prescribed or taken multiple times (each time for at least 6 months).

Chronic Occlusion

An occlusion presumed to have been present for at least 1 month prior to the procedure.

- **Total Occlusion:**

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

- **Sub-total Occlusion:**

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

Clinical Device Failure

A device is said to have failed if it did not meet the requirements of the definition for clinical device success. *See also:* **Clinical Device Success** and **Clinical Procedure Success**

Clinical Device Success

Achievement of a final in-stent residual diameter stenosis of < 50% assessed by online quantitative angiography or visual estimation, using XIENCE V and without a device malfunction. A device is considered to have failed if it did not meet the requirements of the definition for clinical device success. *See also:* **Clinical Procedure Success** and **Clinical Device Failure**.

Clinical Procedure Success

Achievement of a final in-stent diameter stenosis of < 50% by online QCA or visual estimation using XIENCE V EECSS, with or without any adjunctive devices, and without the occurrence of cardiac death, target vessel MI (Q-wave and non Q-wave MI), or repeat revascularization of the target lesion during the health care facility stay. *See also:* **Clinical Device Success**

Composite Endpoint

Composite endpoint is defined by the Academic Research Consortium²⁰ as follows:

- Device-oriented composite includes cardiac death, myocardial infarction attributed to the target vessel, and target lesion revascularization
- Patient-oriented composite includes all-cause mortality, any myocardial infarction, and any repeat revascularization (includes all target and non-target vessel)

Coronary Artery Bypass Graft (CABG) Surgery

Acute CABG surgery is defined as immediate transfer from the catheterization laboratory to the operative room for emergent bypass surgery during the initial treatment phase. Coronary artery bypass graft surgery during follow-up is only considered as a target vessel revascularization and major adverse coronary event if coronary angiography indicates a diameter of stenosis >50% of the stented coronary segment associated with one of the following conditions:

- A positive history of recurrent angina pectoris presumably related to the target vessel
- Objective signs of ischemia (exercise test or equivalent) presumably related to the target vessel
- Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve)

CVA

Please see **Stroke or Cerebrovascular Accident**.

Death

Death defined by the Academic Research Consortium²⁰ is as follows:

All death is considered to be cardiac death unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (eg, cancer, infection) should be classified as cardiac.

Cardiac death

Any death due to proximate cardiac cause (eg, myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Vascular death

Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

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.

Device Malfunction

Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. See also: **Unanticipated Adverse Device Effect (UADE)**

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

Enrolled Patient

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent and only XIENCE V EECSS stent(s) is (are) received during the index procedure.

Epicardial Vessels

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

In-stent

Within the stent margins

In-segment

Within the stent margins and 5 mm proximal and 5 mm distal to the stent

Late Loss (LL)

Late loss is calculated as follows:

Minimum lumen diameter (MLD) post-procedure – MLD at follow-up

- **In-segment Late Loss:** in-segment MLD post-procedure – in segment MLD at follow-up
- **In-stent Late Loss:** in-stent MLD post-procedure – in-stent MLD at follow-up
- **Proximal Late Loss:** proximal MLD post-procedure – proximal MLD at follow-up where proximal = within 5 mm of healthy tissue proximal to stent placement

- **Distal Late Loss:** distal MLD post-procedure – distal MLD at follow-up where distal = within 5 mm of healthy tissue distal to stent placement

LL

Please see **Late Loss**

Major Bleeding Complications

Please see Bleeding/Hemorrhagic Complications

MI

Please see Myocardial Infarction

MLD

Please see Minimum Lumen Diameter

Minimum Lumen Diameter (MLD)

The average of 2 orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent, or in segment.

- MLD is visually estimated during angiography by the investigator
- MLD is measured during QCA by the angiographic core laboratory

Myocardial Infarction (MI)

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Academic Research Consortium²⁰ as follows:

Classification	Biomarker Criteria*	Additional Criteria
Periprocedural PCI	Troponin > 3 x URL or CK-MB > 3 x URL	Baseline value <URL
Periprocedural CABG	Troponin > 5 x URL or CK-MB > 5 x URL	Baseline value <URL and any of the following: new pathologic Q waves or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium
Spontaneous	Troponin > URL or CK-MB > URL	
Sudden death	Death before biomarkers obtained or before expected to be elevated	Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus

		by angiography or autopsy
Reinfarction	Stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after second sample diagnose recurrent MI	If biomarkers increasing or peak not reached then insufficient data to diagnose recurrent MI

URL = Upper Reference Limit (defined 99th percentile of normal reference range);

LBBB = Left Bundle-branch Block

* Baseline biomarker value requiring before study procedure and presumes a typical rise and fall

- **Periprocedural MI After PCI**

The periprocedural period includes the first 48 hours after percutaneous coronary intervention.

- **Periprocedural MI After CABG**

The periprocedural period includes the first 72 hours after coronary artery bypass CABG grafting.

- **Spontaneous MI**

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

With the unique issues and pathophysiological mechanisms associated with these later events as well as the documented adverse impact on short-and long-term prognosis, a more sensitive definition than for periprocedural MI of any elevation of troponin above the upper range limit is used. All late events that are not associated with a revascularization procedure simply as spontaneous.

- **Electrocardiographic Classification**

Within this category Q-wave MI and Non Q-wave MI are distinguished as follows:

- Q-wave MI: Development of new pathologicals in 2 or more contiguous leads (according to the Minnesota code as assessed by the ECG core laboratory) with or without post-procedure CK or CK-MB levels elevated above normal.
- Non Q-wave MI: All MIs not classified as Q-wave.

- **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.

Non-cardiovascular Death

Please see **Death**

No-Reflow

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

Non-TLR

Please see Revascularization

Non-TVR

Please see Revascularization

PCI

Please see Percutaneous Coronary Intervention

Percent Diameter Stenosis (% DS)

The value calculated by the following:

$$100 * (1 - \text{minimum lumen diameter} / \text{reference vessel diameter})$$

using the mean values from 2 orthogonal views (when possible) determined by quantitative coronary angiography.

Percutaneous Coronary Intervention (PCI)

Refers to all interventional cardiology procedures used to treat coronary artery disease.

Permanent Impairment

Permanent impairment means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Principal Investigator

A physician-specialist responsible for overseeing trial conduct at all sites, protocol compliance, and relevant FDA regulations

Primary Investigator

A physician responsible for conducting the study at each investigational site

Reference Vessel Diameter (RVD)

An approximation of the target lesion vessel diameter. The reference vessel diameter is visually estimated during angiography by the investigator and it is measured using quantitative coronary angiography by the angiographic core laboratory.

Restenosis

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

Revascularization

Revascularization is defined by the Academic Research Consortium²⁰ as follows:

- **Target Lesion Revascularization (TLR)**

Target lesion revascularization 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 target lesion revascularizations should be classified prospectively as clinically indicated* or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

- **Target Vessel Revascularization (TVR)**

Target vessel revascularization 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 a lesion other than the target lesion is considered a non target lesion revascularization.

- **Non Target Vessel Revascularization (non-TVR)**

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

***Clinically indicated revascularization**

A revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis $\geq 50\%$ (core laboratory quantitative coronary angiography assessment) and if one of the following occurs:

- (1) A positive history of recurrent angina pectoris, presumably related to the target vessel;
- (2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;
- (3) Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve);
- (4) A TLR or TVR with a diameter stenosis $\geq 70\%$ even in the absence of the above-mentioned ischemic signs or symptoms.

RVD

Please see Reference Vessel Diameter

SAE

Please see Serious Adverse Event

Serious Adverse Event (SAE)

A fatal or serious deterioration in health involving the following:

- A life-threatening event;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization;
- An event resulting in a persistent or significant disability/incapacity;
- An event resulting in a congenital anomaly/birth defect;
- An event that is medically important that may not result in death, be life-threatening, require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient and/or may require intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

See also: Adverse Event, Unanticipated Adverse Device Effect

Serious Injury

Serious injury is an injury or illness that

- is life-threatening;
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Stent Thrombosis

Stent thrombosis is defined and discussed by the Academic Research Consortium²⁰ as follows:

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject left the catheterization laboratory.

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.

Stent Thrombosis Categories: a) Definite b) Probable, and c) Possible

a) Definite stent thrombosis

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

Angiographic confirmation of stent thrombosis*

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

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

*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.

Pathological confirmation of stent thrombosis

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

b) 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.

c) 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 or Cerebrovascular Accident (CVA)

A syndrome characterized by the acute onset of a neurological deficit that persists for at least 24 hours, reflects focal involvement of the central nervous system, and is the result of a disturbance of the cerebral circulation, due to ischemia or hemorrhage.

Target Lesion

A lesion to be treated during the index procedure

Target Vessel

The entire epicardial vessel containing the treated lesion

Thrombosis in Myocardial Infarction (TIMI) Flow Grades ²¹

Thrombosis in Myocardial Infarction flow grades are defined by the following:

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

TIA

Please see **Transient Ischemic Neurological Attack**

TIMI

Please see **Thrombosis in Myocardial Infarction Flow Grades**

TLR

Please see **Revascularization**

Total occlusion

Please see **Chronic Occlusion**.

Transient Ischemic Neurological Attack (TIA)

A sudden onset of reversible focal neurological deficits due to vascular lesions of the brain that lasts ≤ 24 hours

TVR

Please see Revascularization

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21 CFR 812.3(s)). See also: **Adverse Event, Anticipated Adverse Event, and Serious Adverse Event**

UADE

Please see Unanticipated Adverse Device Effect

Vascular Death

Please see **Death**

XIENCE V EECSS Pivotal Study III and IV

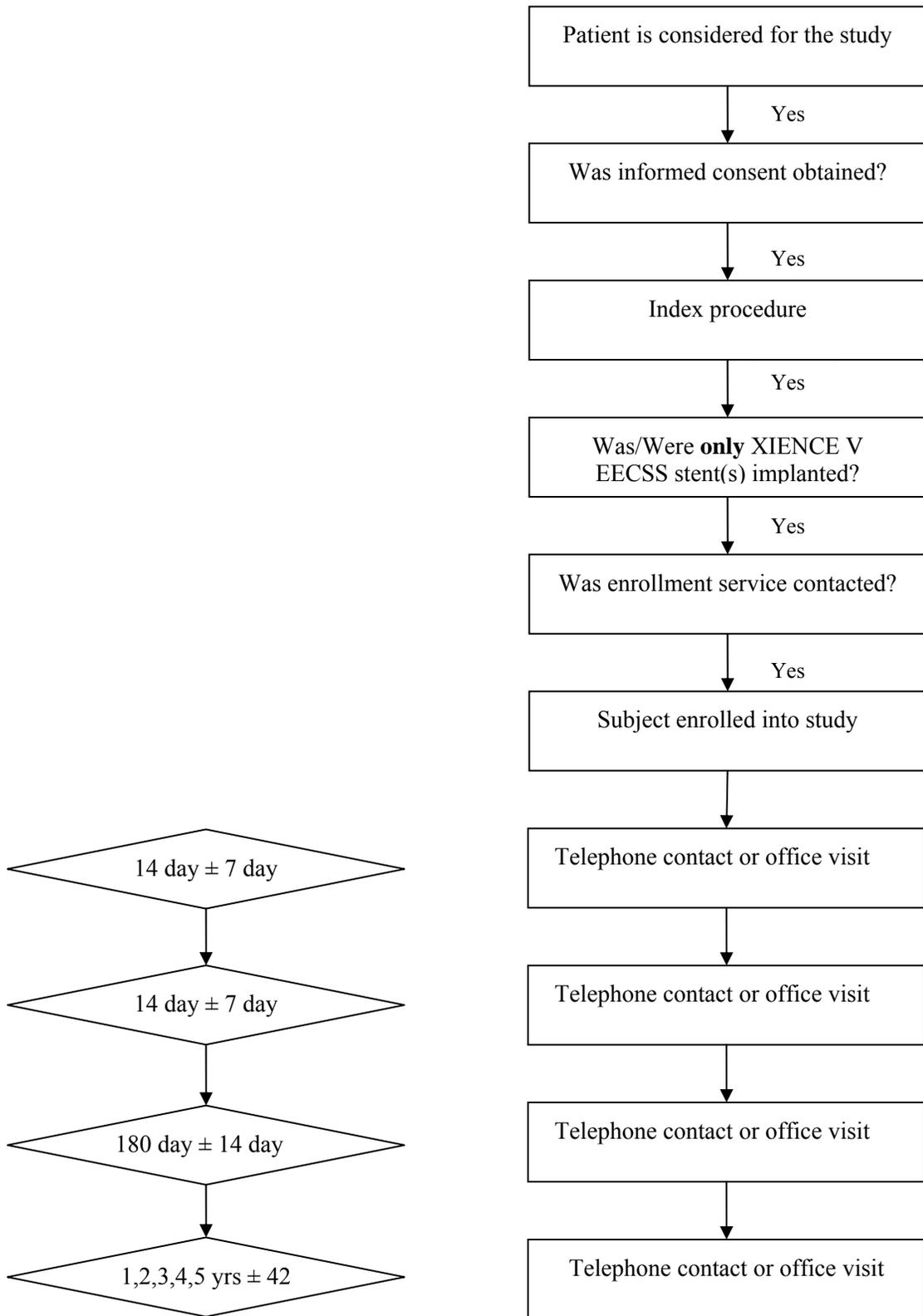
FDA approved clinical trials examining XIENCE V EECSS safety and efficacy sponsored by Abbott Vascular. XIENCE V EECSS Pivotal Study III and IV are also known as SPIRIT III and IV. *See also* Appendix V XIENCE V EECSS Pivotal Study Eligibility Criteria

17.2 Appendix II Acronyms and Abbreviations

Acronym/ Abbreviation	Term
%DS	Percent Diameter Stenosis
AE	Adverse Event
AMI	Acute Myocardial Infarction
APOAI	Apolipoprotein A1
APOB	Apolipoprotein B
ARC	Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CEC	Clinical Events Committee
CI	Clinically Indicated
CK	Creatine Kinase
CK-MB	Creatine Kinase Myocardial-Band Isoenzyme
cm	Centimeter
COURAGE	Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation
CSS	Coronary Stent System
CTO	Chronic Total Occlusion
CVA	Cerebral Vascular Accident
DES	Drug Eluting Stent
dL	Deciliter
DS	Diameter Stenosis
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EECSS	Everolimus Eluting Coronary Stent System
FDA	Food and Drug Administration
g	grams
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA _{1c}	Hemoglobin A _{1c}
Hct	Hematocrit
HDL	High Density Lipoprotein
Hgb	Hemoglobin
IRB	Institutional Review Board
IFU	Instructions for Use
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery

Acronym/ Abbreviation	Term
LCX	Left Circumflex Coronary Artery
LL	Late Loss
µg	Microgram
MACE	Major adverse coronary event
mg	Milligram
MDR	Medical Device Reporting
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
mm	Millimeter
PCI	Percutaneous Coronary Intervention
POBA	Plain Old Balloon Angioplasty
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
RCT	Randomized Clinical Trial
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
TAXUS PECSS	TAXUS® EXPRESS ² ™ Paclitaxel Eluting Coronary Stent System
TIA	Transient Ischemic Neurological Attack
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
URL	Upper Reference Limit
UADE	Unanticipated Adverse Device Effects
USA	United States of America
VO	Volume Obstruction
WBC	White Blood Cell Count
XIENCE V USA	XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) USA Post-Approval Registry

17.3 Appendix III Trial Flow



17.4 Appendix IV Schedule of Events

	Baseline (4 weeks prior to index Procedure)	Pre-Procedure	Procedure	Post-Procedure	14 days (± 7 d) phone contact or office visit	30 days (± 7 d) phone contact or office visit	180 days (± 14 d) phone contact or office visit	1, 2, 3, 4, & 5yr (± 42 d) phone contact or office visit
Informed consent	✓							
Demographic: age, gender, race	✓ ¹							
Medical Hx: cardiac, diabetes mellitus, hypertension, dyslipidemia, CABG, PCI, renal insufficiency, anemia	✓ ¹							
Socioeconomic Status: marital status, education, employment, health care access	✓ ¹							
Physical Measurements: weight, height, waist, hip circumference, blood pressure	✓ ¹							
Other Risk Factors: tobacco use, familial CAD, stroke	✓ ¹							
Seattle Angina Questionnaire	✓ ²						✓	✓ ⁴
Laboratory Assessment: WBC, platelet count, HbA _{1c} , Hb, Hct, lipid profile (LDL, HDL, triglycerides, total cholesterol), APOAI/APOB, serum insulin/serum glucose (fasting or random), creatinine	✓							
CK, CK-MB, and/or troponin		✓		✓ ³				
ECG		✓		✓ ³				
Pivotal- Study Eligibility Criteria	✓ ¹							
Antiplatelet loading dose		✓ ⁵						
Stent use attributes and lesion characteristics, product performance			✓					
Coronary angiogram				✓				
Hospital discharge instruction				✓				
Antiplatelet therapy, chronic concomitant medications	✓			✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓	✓

1. Baseline or post procedure if not collected at baseline 2. Baseline or anytime prior to discharge no later than 14 days post procedure 3. Immediately post-procedure 4. 1 year follow-up only 5. Loading dose administered at pre or during procedure

17.5 Appendix V XIENCE V EECSS Pivotal Study Eligibility Criteria

17.5.1 General Inclusion Criteria

1. Subject must be at least 18 years of age
2. Subject must have evidence of myocardial ischemia (eg, stable or unstable angina, silent ischemia, positive functional study or a reversible change in the electrocardiogram (ECG) consistent with ischemia)
3. Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery
4. Subject must agree not to participate in any other clinical study for a period of one year following the index procedure

17.5.2 Angiographic Inclusion Criteria

1. Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥ 2.5 mm to ≤ 4.25 mm.

XIENCE V Pivotal study III RCT: If two target lesions meet the inclusion criteria they must be in different epicardial vessels

XIENCE V Pivotal study IV: treatment of up to three *de novo* target lesions, maximum of two *de novo* target lesions per epicardial vessel

2. Target lesion(s) must measure ≤ 28 mm in length by visual estimation
3. If more than one target lesion will be treated, the RVD and lesion length of each must meet the above criteria
4. The target lesion(s) must be in a major artery or branch with a visually estimated stenosis of $\geq 50\%$ and $< 100\%$ with a TIMI flow of ≥ 1
5. Intervention prior to index procedure:

XIENCE V Pivotal study III RCT (Non-Target Vessel): Non-study, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥ 90 days prior to the index procedure (Patients receiving brachytherapy in a non-target epicardial vessel will however, be excluded from the trial)

XIENCE V Pivotal study IV (Target Vessel): Non-study, percutaneous intervention for lesions in a target vessel (including side branches) is allowed if done ≥ 9 months prior to the index procedure

XIENCE V Pivotal study IV (Non-Target Vessel): Non-study percutaneous intervention for lesions in a non-target vessel involving:

- a. Successful and uncomplicated (visually estimated diameter stenosis $< 50\%$, TIMI Grade-3 flow, no ECG changes, prolonged chest pain, or angiographic complications) bare metal stent, balloon dilatation, cutting balloon, atherectomy, thrombectomy, and laser treatments are allowed if done ≥ 24

hours prior to the index procedure or during (before randomization) the index procedure. For interventions done within 24 to 48 hours prior to the index procedure, CK and CK-MB must be assessed to be < 2 times the upper limit of normal at the time of the index procedure. NOTE: Procedures within the 24 hour period preceding the index procedure are not permitted

- b. Unsuccessful or complicated bare-metal stent, balloon dilatation, cutting balloon, atherectomy, thrombectomy, and laser treatments are allowed if done ≥ 30 days prior to the index procedure
 - c. Drug-eluting stent treatment is allowed if done ≥ 90 days prior to the index procedure
6. Non-study, percutaneous interventions for lesion(s) in a target vessel (including side branches) or non-target vessel are allowed if done ≥ 9 months after the index procedure

17.5.3 General Exclusion Criteria

1. Subject has had a known diagnosis of acute myocardial infarction (AMI) preceding the index procedure (CK-MB ≥ 2 times upper limit of normal) and CK and CK-MB have not returned within normal limits at the time of procedure
2. The subject is currently experiencing clinical symptoms consistent with AMI
3. Subject has current unstable arrhythmias
4. Subject has a known left ventricular ejection fraction (LVEF) < 30%
5. Subject has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant
6. Subject is receiving or scheduled to receive anticancer therapy for malignancy within 30 days prior to or after the procedure
7. Subject is receiving immunosuppression therapy, or has known serious immunosuppressive disease (eg, human immunodeficiency virus), or has severe autoimmune disease that requires chronic immunosuppressive therapy (eg, systemic lupus erythematosus, etc.)
8. Subject is receiving or is scheduled to receive chronic anticoagulation therapy (eg, heparin, coumadin)
9. Subject has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, both clopidogrel and ticlopidine, everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated
10. Elective surgery that will require discontinuing either aspirin or clopidogrel is planned within the first 9 months after the procedure

11. Subject has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³, a WBC of $< 3,000$ cells/mm³, or documented or suspected liver disease (including laboratory evidence of hepatitis)
12. Subject has known renal insufficiency (eg, serum creatinine level of > 2.5 mg/dL or subject on dialysis)
13. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
14. Subject has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months
15. Subject has had a significant GI or urinary bleed within the past six months
16. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion
17. Subject has other medical illness (eg, cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-compliance with the protocol, confound the data interpretation or is associated with a life expectancy of less than one year
18. Subject is already participating in another clinical study that has not yet reached its primary endpoint
19. Pregnant or nursing patients and those who plan pregnancy in the period up to 1 year following index procedure. (Female patients of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure and effective contraception must be used up to 1 year following the index procedure)

17.5.4 Angiographic Exclusion Criteria

1. The target lesion(s) meets any of the following criteria:
 - a. Left main coronary artery location including left main ostial location (NOTE: RCA-aorto-ostial lesions are not excluded)
 - b. Located within 2 mm of the origin of the LAD or LCX
 - c. Located within an arterial or saphenous vein graft or distal to a diseased (vessel irregularity per angiogram and any visually estimated diameter stenosis $> 20\%$) arterial or saphenous vein graft
 - d. Involves a bifurcation in which the side branch is ≥ 2 mm in diameter AND the ostium of the side branch is $> 50\%$ stenosed by visual estimation
 - e. Involves a side branch requiring pre-dilatation
 - f. Total occlusion (TIMI flow 0) prior to wire crossing
 - g. Excessive tortuosity proximal to or within the lesion
 - h. Extreme angulation ($\geq 90^\circ$) proximal to or within the lesion
 - i. Heavy calcification
 - j. Restenotic from previous intervention

- k. **Pivotal study III only:** Located in a major epicardial vessel or a side branch that has been previously treated with any type of PCI (eg, POBA, stent, cutting balloon, atherectomy), < 9 months prior to the index procedure
- 2. Subject has received brachytherapy in any epicardial vessel (including side branches)
- 3. The target vessel contains thrombus
- 4. Another clinically significant lesion in the target vessel is present that requires or has a high probability of requiring PCI during the index procedure
- 5. Another lesion in a target or non-target vessel (including all side branches) is present that requires or has a high probability of requiring PCI within 9 months after the index procedure

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