FDA Executive Summary

Prepared for the
March 15, 2016 meeting of the
Circulatory System Devices Advisory Panel

P150023

Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System

INTRODUCTION

This is the FDA Executive Summary for a first-of-a-kind, fully absorbable drug-eluting coronary stent, the Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System (referred to herein as the BVS). This device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under Premarket Approval (PMA) application P150023, which is the subject of this Advisory Panel meeting.

This memorandum will summarize the FDA's review of the PMA, highlighting the particular areas for which we are seeking the Panel's expertise and input. These topics will include the proposed indications for use, pre-clinical study findings, the results from the randomized pivotal clinical trial, additional clinical studies conducted by the sponsor, and the proposed post-approval study. At the conclusion of your review and discussion of the data presented, the Agency will ask for the Panel's recommendation regarding whether or not the data demonstrate a reasonable assurance of safety and effectiveness of the BVS.

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LIST OF ABBREVIATIONS

ABR – Angiographic Binary Restenosis
AE – Adverse Event
API – Active Pharmaceutical Ingredient
ARC – Academic Research Consortium
AT – As-treated
AUC – Area Under the Curve
BVS – Bioresorbable Vascular Scaffold
CABG – Coronary Artery Bypass Graft
CEC – Clinical Events Committee
CK-MB – Creatine Kinase Myocardial Band
C_{max} – Maximum Concentration
CRF – Case Report Form
CT – Computed Tomography
D_{max} – Maximum Diameter
DM – Diabetes Mellitus
DMF – Drug Master File
DMR – Death, MI, and revascularization
ECG – Electrocardiogram
FFR – Fractional Flow Reserve
GFR – Glomerular Filtration Rate
GLP – Good Laboratory Practice
ID-TLR – Ischemia-Driven Target Lesion Revascularization
ITT – Intent-to-Treat
ITDM – Insulin-treated Diabetes Mellitus
IVUS – Intravascular Ultrasound
LAD – Left Anterior Descending Coronary Artery
LCX – Left Circumflex Coronary Artery
LLL – Late Lumen Loss
LMCA – Left Main Coronary Artery
LVEF – Left Ventricular Ejection Fraction
MI – Myocardial Infarction
MLD – Mean Lumenal Diameter
MSCT – Multi-Slice Computed Tomography
MTDM – Medically Treated Diabetes Mellitus
NITDM – Non-insulin Treated Diabetes Mellitus
NMTDM – Non-medically Treated Diabetes Mellitus
NQMI – Non-Q-wave Myocardial Infarction
OCT – Optical Coherence Tomography
ODS – Optimized Delivery System

PDLLA – Poly (D,L-lactide)
PK – Pharmacokinetics
PLLA – Poly (L-lactide)
PP – Per-protocol
PRO – Patient-Reported Outcome
PTE – Per-Treatment-Evaluable
QCA – Quantitative Coronary Angiography
QMI – Q-wave Myocardial Infarction
RDS – Rose Dyspnea Scale
RVD – Reference Vessel Diameter
RX – Rapid Exchange
SAE – Serious Adverse Event
SAQ – Seattle Angina Questionnaire
SEM – Standard Error of the Mean
TIMI – Thrombolysis in Myocardial Infarction
TLF – Target Lesion Failure
TLR – Target Lesion Revascularization
TVF – Target Vessel Failure
TVR – Target Vessel Revascularization
TVMI – Target Vessel Myocardial Infarction
ULN – Upper Limit of Normal
WHO – World Health Organization

1 PROPOSED INDICATIONS FOR USE

The sponsor has proposed the following Indication for Use:

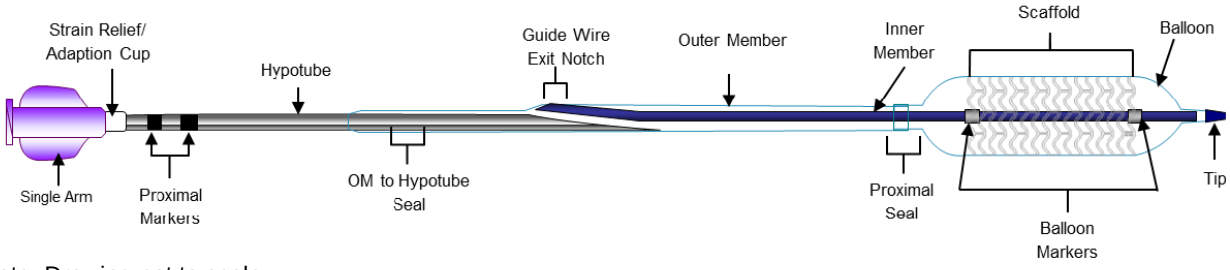
> *The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) is a temporary scaffold that will fully resorb over time and is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to* de novo *native coronary artery lesions (length ≤24 mm) with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm.*

2 DEVICE DESCRIPTION

The ABSORB GT1 BVS System (see Figures 1 and 2) is a drug/device combination product consisting of the following components:

- Balloon dilatation catheter (Delivery System)
- An absorbable polymeric (poly (L-lactide), PLLA) scaffold
- A drug-eluting coating
  - Absorbable polymer (poly (D,L-lactide), PDLLA)
  - Anti-proliferative/immunosuppressant drug (everolimus)

Please refer to Figures 2-1 and 2-2 for a visual description of the GT1 BVS.



Note: Drawing not to scale

Figure 2-1. Absorb GT1 BVS System

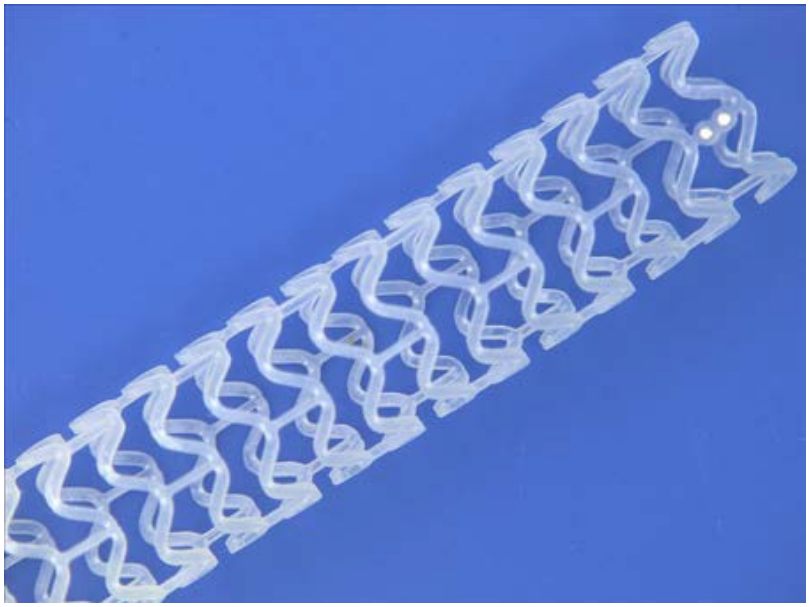


Figure 2-2. Digital Photograph of the 3.5 mm Medium BVS in Expanded Form

2.1 Balloon Dilatation Catheter (Delivery System)

The GT1 BVS delivery system is a rapid-exchange (RX) design, where the balloon and scaffold are located at the distal end of the catheter. The proximal lumen allows for inflation of the balloon with contrast medium and the central distal lumen is used for guidewire insertion to facilitate advancement of the catheter within the vasculature. The distal catheter shaft, the tip, and tapers of the balloon are coated with HYDROCOAT™ Hydrophilic Coating.

Radiopaque markers are located under the balloon at either end to enable fluoroscopic visualization. There are also markers on the proximal outer shaft of the catheter to help the physician gauge the delivery catheter position relative to the guiding catheter tip. An adaption arm on the proximal end provides access to the inflation lumen. It also includes a luer-lock fitting to facilitate connection to an inflation device. The various design features of the GT1 BVS delivery system are illustrated in Figure 2-1.

The only difference between the Absorb GT1 BVS System and the Absorb BVS System investigated in the clinical studies under the IDE is that the GT1 BVS System has a modified delivery system, referred to as an optimized delivery system (ODS) by the sponsor. The ODS is similar to the delivery system used in the FDA-approved XIENCE Alpine with minor modifications to accommodate the BVS; and the delivery system used on the IDE BVS is similar to that used in the MULTI-LINK VISION® Rapid Exchange (RX) Coronary Stent System, with minor modifications made to accommodate the BVS. The ODS was implemented to improve device pushability. The sponsor performed bench testing on the GT1 BVS to demonstrate that the BVS using the ODS performed as expected. The design modifications were not significant enough to warrant additional clinical testing. Therefore, FDA has no outstanding concerns about the GT1 delivery system.

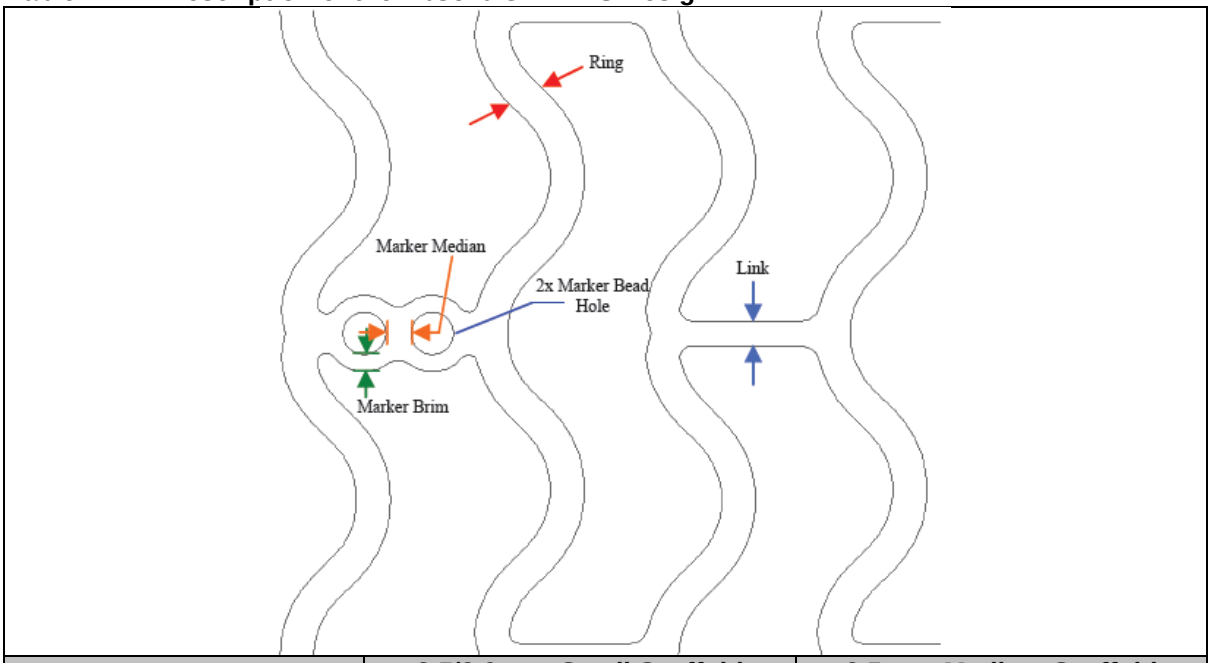
2.2 Scaffold Component

The GT1 BVS scaffold design consists of a series of circumferentially-oriented sinusoidal rings that are connected to neighboring rings by three linear links. The product matrix has two distinct

designs, the small design (2.5 and 3.0 mm diameter sizes) and the medium design (3.5 mm diameter sizes). Two platinum markers are embedded in each end ring to enable fluoroscopic visualization of the scaffold. Both the small and medium scaffold designs are based on the design principles of Abbott Vascular's metallic balloon expandable stents (MULTI-LINK and XIENCE family of products).

The various design features of the GT1 BVS are summarized in Table 2.2-1.

Table 2.2-1. Description of the Absorb GT1 BVS Design



	2.5/3.0 mm Small Scaffold	3.5 mm Medium Scaffold
Expansion	Balloon expandable	
Backbone Material	Poly(L-lactide)	
Scaffold Coating	Antiproliferative Drug – Everolimus Controlled Drug Release Polymer – Poly(D,L-Lactide)	
Permanent Scaffold Markers	Platinum	
Expansion Diameter (mm)	2.5 (Max post-dil 3.0) 3.0 (Max post-dil 3.5)	3.5 (Max post-dil 4.0)
Length (mm)	8, 12, 18, 23, 28	12, 18, 23, 28
Scaffold Free-Area Percentage for 18 mm length	68% at 2.5 mm expansion 73% at 3.0 mm expansion	73% at 3.5 mm expansion
Number of Crests per Ring	6	
Number of Links Between Rings	3	
Strut Width (mm)	Ring: 0.1905 (0.0075 inch) Link: 0.1397 (0.0055 inch)	Ring: 0.2159 (0.0085 inch) Link: 0.1397 (0.0055 inch)
Strut Thickness (mm)	0.1575 (0.0062 inch)	
Marker Hole Diameter (mm)	0.2337 (0.0092 inch)	

The differences in the small and medium designs are illustrated in Figure 2.2-1.

a. **b.**

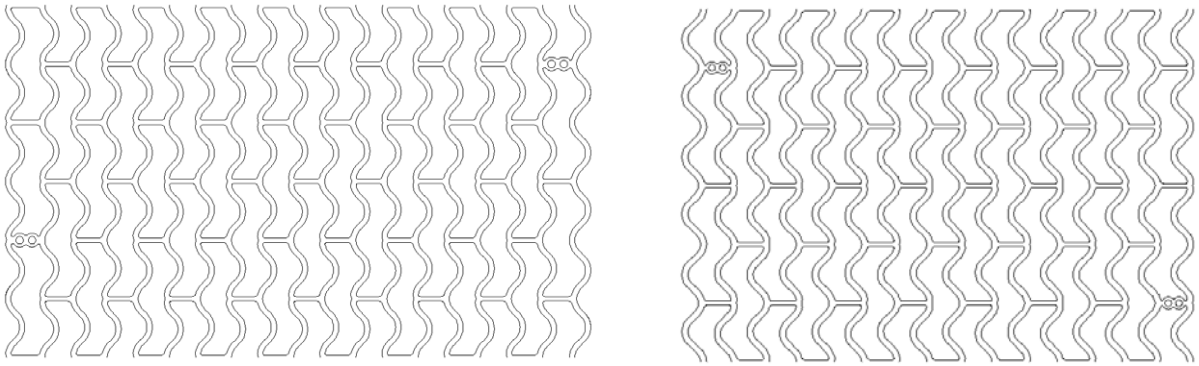


Figure 2.2-1. Representative Absorb GT1 BVS a.) Small Pattern (2.5/3.0 x 18 mm) and b.) Medium Pattern (3.5 x 18 mm)

The scaffold is fabricated from PLLA (Figure 2.2-2), a semi-crystalline absorbable polymer with a high tensile strength and modulus. The thermal properties of PLLA are shown in Table 2.2-2.

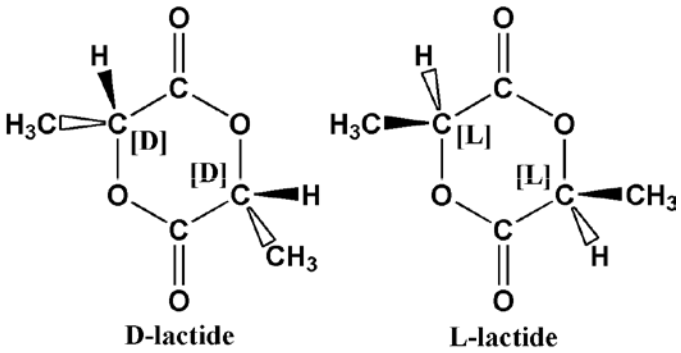


Figure 2.2-2. Chemical Structures of D-lactide and L-lactide

Table 2.2-2. Properties of PLLA

Max Crystallinity	T_m	T_g
~ 70%	170 – 180 °C	55 – 70 °C

T_m – melting temperature
T_g – glass transition temperature

2.3 Drug-Eluting Coating

The GT1 BVS is spray coated with a physical mixture of 50 wt% PDLLA and 50 wt% everolimus, the identical active pharmaceutical ingredient (API) used in the XIENCE family of stents. For additional information on everolimus, please refer to Section 2.3.2. The sponsor also used the same drug dose density (100 µg/cm^2) as the XIENCE family of stents. Table 2.3-1 summarizes the surface area and drug dose density for each stent in the product matrix.

Table 2.3-1. Scaffold Surface Area and Target Drug Amount for the Absorb GT1 BVS System

Scaffold Diameter (mm)	Scaffold Length (mm)	Scaffold Surface Area (cm^2)	Drug Dose Density (µg/cm^2)	Target Drug Amount (µg)
2.5 / 3.0	8	0.76	100	76
	12	1.14		114
	18	1.81		181
	23	2.28		228

Scaffold Diameter (mm)	Scaffold Length (mm)	Scaffold Surface Area (cm^2)	Drug Dose Density ($\mu g/cm^2$)	Target Drug Amount (µg)
3.5	28	2.76		276
	12	1.35		135
	18	1.97		197
	23	2.46		246
	28	3.08		308

2.3.1 Absorbable Polymeric Component

The polymeric portion of the GT1 BVS coating is composed of poly(D,L-lactide), an amorphous polymer containing an equimolar mixture of D- and L-lactide. The chemical structures of D- and L-lactide are illustrated in Figure 2.2-2 above. The purpose of the absorbable polymeric component is to control the release of the drug component.

2.3.2 Drug Component

Everolimus [40-O-(2-hydroxyethyl)-rapamycin] (Figure 2.3-1) is the drug component on the GT1 BVS scaffold, and is an immunosuppressive agent that is intended to prevent smooth muscle cell proliferation within the scaffold. It is manufactured by the Novartis Pharmaceuticals Corporation.

Everolimus is synthesized via chemical modification of rapamycin, a secondary macrolide metabolite produced by certain actinomycete strains. Everolimus is also used on the XIENCE family of DES.

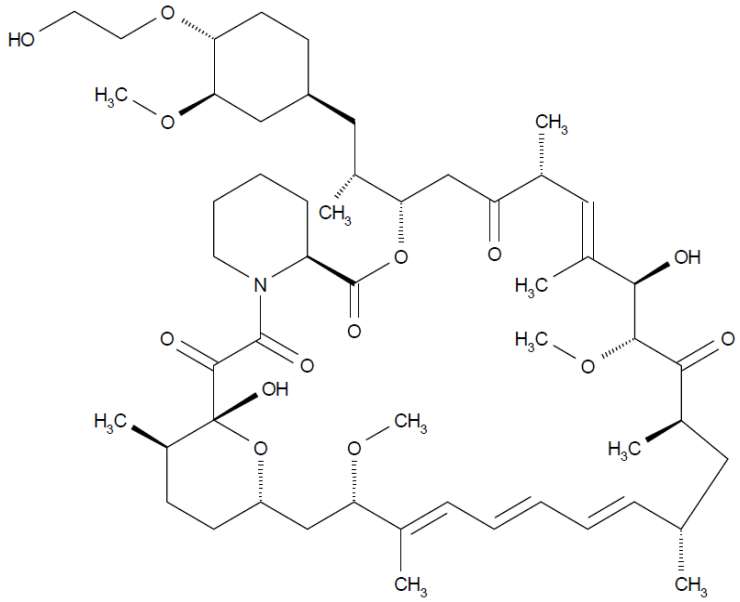


Figure 2.3-1. Structure of Everolimus

2.3.2.1 Drug Mechanism of Action

At the cellular level, everolimus reversibly inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1, two key factors in the initiation of protein synthesis, is inhibited. Everolimus-FKBP-12

complex may also bind to and interfere with the function of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, the mammalian Target Of Rapamycin), a protein that governs cell metabolism, growth and proliferation.

The GT1 BVS product matrix is shown in Table 2.3-2.

Table 2.3-2. Absorb GT1 BVS System Size Matrix

Scaffold Design	Product Diameter (mm)	Product Length (mm)				
		8	12	18	23	28
Small	2.5	X	X	X	X	X
	3.0	X	X	X	X	X
Medium	3.5	N/A	X	X	X	X

N/A – size not available

2.4 Device Mechanism of Action

The BVS is designed to provide temporary arterial mechanical support for an adequate duration after implantation, elute an anti-proliferative drug to prevent restenosis, and ultimately disappear via bioabsorption once arterial support is no longer needed, as depicted in Figure 2.4-1.

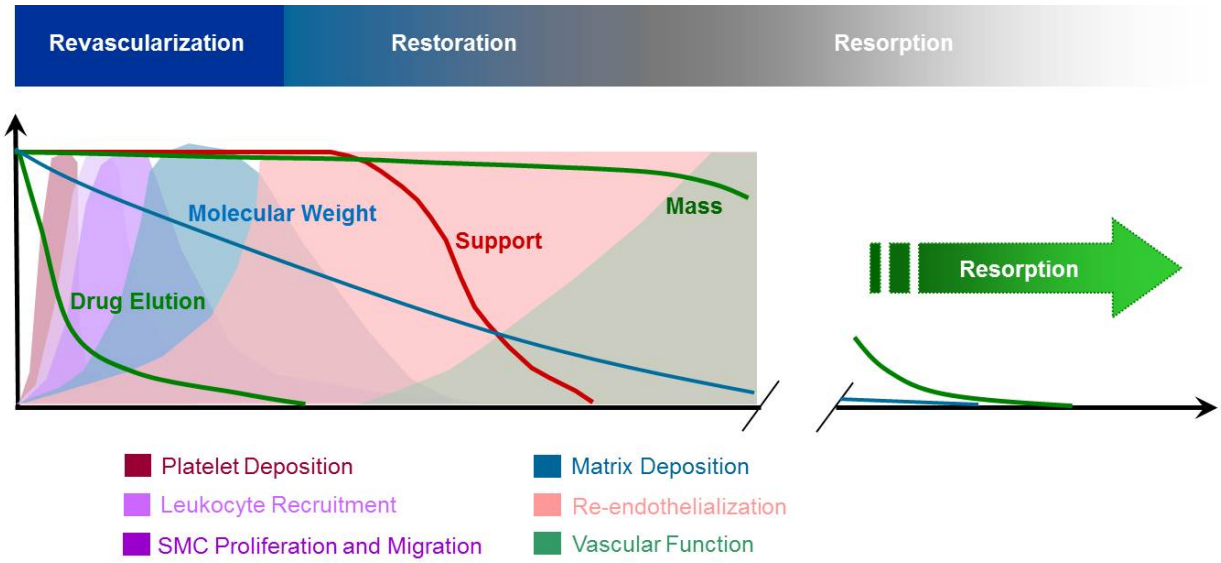


Figure 2.4-1. Schematic Drawing of Three Stages of Device Performance

3 BACKGROUND INFORMATION

Over the last four decades, percutaneous coronary intervention (PCI) has evolved from balloon angioplasty (PTCA) to the current generation of drug-eluting stents (DES). Acute recoil, abrupt arterial closure, and restenosis (due to intimal hyperplasia and negative arterial remodeling) limited PTCA effectiveness. Bare metal stents (BMS) successfully addressed acute recoil, abrupt vessel closure, and negative arterial remodeling but were associated with relatively high rates of restenosis due to intimal hyperplasia. The initial generation of DES that released antiproliferative agents from a polymer coating significantly reduced restenosis rates compared with BMS. However, concerns emerged regarding late stent thrombosis that were likely related to multiple factors including delayed arterial healing requiring long duration dual antiplatelet therapy (DAPT), local arterial reactions to durable polymer coatings, suboptimal stent deployment, and DES (over)use in highly complex patient and lesion subsets. Greater attention to lesion selection and optimal stent implantation techniques, as well as increased patient compliance with prolonged DAPT have lowered the rates of late stent thrombosis. Concurrently, the development of next generation DES with more flexible thinner strut designs (for improved device deliverability) and increasingly biocompatible durable and bioabsorbable polymer coatings have improved the acute and long-term safety and effectiveness of DES. Nevertheless, there remains an approximately 1.5-2% annual rate of late clinical events associated with currently available metallic DES (and BMS) mostly due to restenosis (related to chronic neointimal proliferation or neoatherosclerosis within the stent).[1,2,3]

The Absorb Bioabsorbable Scaffold (BVS) is a fully biodegradable drug-eluting platform, which was engineered based on the principle that a mechanical arterial support device (to prevent vessel recoil and negative remodeling) and anti-proliferative drug elution are needed only for a limited period of time post-PCI; after the vascular healing responses of the treated artery have reached a steady state, the metallic stent is no longer necessary to maintain vessel patency. Further, it has been postulated that the absence of a permanent arterial stent might allow for the restoration of normal vasomotion, late luminal enlargement, favorable plaque modification, more options for future revascularization procedures (if needed), and more opportunities for non-invasive assessment of arterial patency and blood flow. The clinical benefits associated with the potential advantages of a bioabsorbable scaffold compared with a current generation DES remain to be demonstrated in clinical studies.

4 REGULATORY HISTORY

Abbott Vascular Sponsored Non-US Clinical Studies

ABSORB Cohort A

The first-in-human prospective, open-labeled ABSORB Cohort A study enrolled 30 subjects from 4 sites in Europe and New Zealand beginning in March 2006. Subjects received a single 3.0 x 12 mm or 3.0 x 18 mm Absorb Cohort A BVS. At 6 months, late lumen loss was lower compared with historical BMS data but was greater than historical XIENCE stent results. The increased BVS late loss vs. XIENCE was believed to have been due to premature loss of scaffold structural integrity and radial strength. This outcome led to a modification in the BVS design and manufacturing process to improve mechanical performance and prolong the duration of effective scaffolding.

Since the Cohort A device was significantly modified to produce the finalized version of the BVS used in the clinical studies to support the PMA, the Cohort A study will not be further reviewed in this executive summary.

ABSORB Cohort B

The single arm, open-labeled ABSORB Cohort B Study enrolled 101 subjects in Europe, Australia, and New Zealand beginning in March 2009. ABSORB Cohort B enrolled subjects with up to two *de novo* native coronary lesions in separate epicardial vessels with visually estimated vessel diameters of 3.0 mm and lesion length ≤14 mm treated with a single 3.0 x 18 mm BVS. Group 1 subjects (n=45) underwent follow-up imaging at 180 days and 2 years, and Group 2 subjects (n=56) underwent follow-up imaging at 1 year and 3 years. The angiographic late loss was 0.18 mm at 6 months for Group 1 and 0.27 mm at 1 year for Group 2, providing evidence that the modified scaffold offered improved radial support. Additional clinical findings at 5 years were an 11% MACE rate and no cardiac deaths or scaffold thromboses with only 7.4% of subjects taking DAPT at 5 years. Serial intravascular ultrasound (IVUS) studies demonstrated late lumen enlargement and increase in scaffold area at 2 years in Group 1 subjects and at 3 years in Group 2 subjects. Serial OCT studies showed resorption of the scaffold struts over time with complete resorption at 5-years. Restoration of vasomotion and the feasibility of performing non-invasive multi-slice CT imaging were also demonstrated.

The Cohort B device is generally similar in design to the version of the BVS used in the ABSORB III pivotal trial with the BVS having slightly thicker struts resulting in a lower scaffold-free area and a higher total scaffold surface area.

ABSORB EXTEND

The single arm, open-label ABSORB EXTEND study is a global continued access registry initiated to expand the treatment of subjects with the BVS in broader geographies and patient populations (*e.g.*, subjects with longer lesions treated with a longer length BVS or overlapping scaffolds). Subjects could have a maximum of two *de novo* native coronary artery lesions (each located in different epicardial vessels). A target lesion length >22 and ≤28 mm was to be treated by overlapping two BVS. There were 812 subjects enrolled at 56 sites (Europe, Australia, Canada, Africa, South America and Asia) beginning in November 2009. At the latest database lock (January 21, 2015), all subjects have been completed 1-year follow-up, and 634 subjects and 476 subjects have been completed 2 and 3-years follow-up, respectively. TVF and MACE rates at 1 year were 5.5% and 5.0%, respectively. There were no cases of acute stent thrombosis (ST). The definite plus probable sub-acute, late, and very late (366-758 days) ST rates were 0.6%, 0.4% and 0.5%, respectively. The cumulative definite plus probable ST rates were 1.0%, 1.3%, and 2.1% for 1, 2, and 3 years, respectively.

ABSORB II

The ABSORB II Trial enrolled 501 subjects from 46 investigational sites in Europe and New Zealand beginning in November 2011. Subjects were randomized to the BVS (335 subjects) or the XIENCE stent (166 subjects). The co-primary endpoints are vasomotor function (the change in mean lumen diameter between pre- and post-intracoronary nitrate infusion) at 3 years and minimum lumen diameter changes from post-procedure to 3 years. At 1-year, there were no cardiac deaths in either treatment group. The target vessel failure (TLF) rate was 4.8% (16/331) in the BVS group and 3.0% (5/165) in the XIENCE group. The cardiac death plus all MI rate in the BVS group was 4.5% (15/331) vs. 1.2% (2/165) in the XIENCE group; the event rate difference was driven by a higher rate of peri-procedural MIs in the BVS group. The ischemia-driven TLR

(ID-TLR) rate 1.2% (4/331) in the BVS group and 1.8% (3/165) in the XIENCE group.

ABSORB Japan RCT

The ABSORB Japan RCT (pivotal trial for approval in Japan) is a prospective, randomized (2:1 Absorb BVS to XIENCE), single-blinded, multicenter clinical trial in a Japanese population. This trial shares several design features with ABSORB III (including the primary TLF endpoint, inclusion and exclusion criteria, and subject follow up). In addition, follow-up angiography will be performed in all subjects at 13 months, and there is an IVUS subgroup (n=150), OCT subgroup (125 subjects in OCT 1 and 125 subjects in OCT 2) and a follow-up vasomotion study subgroup. Beginning in April 2013, 400 subjects from 38 investigational sites in Japan were enrolled and randomized to the BVS group (266 subjects) or the XIENCE group (134 subjects). TLF at 1 year was 4.2% (11/265) in the BVS group vs. 3.8% (5/133) in the XIENCE group, which met statistical non-inferiority (with a non-inferiority margin of 8.6%). There were no cardiac deaths in either treatment group. The target vessel MI rates were 3.4% (9/265) and 2.3% (3/133), and the ID-TLR rates were 2.6% (7/265) and 2.3% (3/133) in the BVS and XIENCE groups, respectively. Cumulative ST rates at 1 year were 1.5% in both groups.

Please also see Appendices 3 to 6 for further information on the non-US BVS studies. *Please note that FDA did not review the clinical study protocols for these non-US studies prior to their initiation.*

Abbott Vascular Sponsored US Clinical Trials

ABSORB III

The US pivotal IDE clinical trial for the Absorb BVS is the ABSORB III trial. The initial Pre-Submission meeting was held between Abbott Vascular and FDA on March 26, 2009 to discuss non-clinical testing requirements and US pivotal trial design. A series of pre-submission meetings took place over the next several months leading to FDA approval of the Absorb III IDE (G120002) on December 14, 2012. The first Lead-In subject was registered on December 28, 2012, followed by enrollment of the first randomized patient in the Primary Analysis Group on March 22, 2013. For the Primary Analysis Group, the last 1-year follow-up visit occurred on April 2, 2015.

The ABSORB III trial outcomes at 1 year are the primary focus of FDA's evaluation of the PMA. Beyond 1 year, ABSORB III outcomes data remain blinded and will be included in analysis of ABSORB IV outcomes data (see ABSORB IV).

ABSORB IV

ABSORB IV is a prospective randomized controlled trial that began enrollment after completion of the enrollment of the ABSORB III trial primary analysis subject cohort. ABSORB IV will enroll 3000 subjects, randomized 1:1 to the BVS or the XIENCE stent. The study inclusion and exclusion criteria are generally similar to ABSORB III. The primary endpoints of ABSORB IV are: (1) the percentage of patients who experienced angina within 1 year; and (2) the target lesion failure (TLF) rate between 1 and 5 years (landmark analysis). The landmark analysis will pool ABSORB IV subjects with the 2008 subjects from the ABSORB III primary analysis group. As of February 2016, 1498 ABSORB IV subjects have been randomized. Enrollment is expected to be complete in December 2016. An interim look with a median 4-year follow-up of 5000 subjects is expected in July 2019, and the planned final data analysis with a median 5-year follow-up for 5000 patients is expected to follow in July 2020.

Since ABSORB IV trial is still in progress and outcome data beyond 1 year data from ABSORB III subjects are being used to address the TLF landmark analysis in ABSORB IV, 2-year ABSORB III data have neither been submitted to nor reviewed by FDA.

The PMA submission for Absorb GT1 BVS was received by FDA on July 1, 2015. During the course of our review of the Absorb GT1 BVS PMA, FDA determined that an Advisory Panel Meeting was warranted to provide FDA with expert opinion on the safety and effectiveness of the Absorb BVS prior to rendering a final decision on the PMA.

5 NON-CLINICAL STUDIES

The sponsor conducted *in vitro* performance and characterization studies of the GT1 BVS, including *in vitro* bench testing, chemistry/manufacturing evaluation, biocompatibility, animal studies and toxicity testing.

5.1 *In Vitro* Bench Testing

Device Performance Testing
There are no guidance documents specifically applicable to drug-eluting stents containing absorbable materials; however, the sponsor used the "*Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*" (Bare Metal Stent Guidance) and the draft guidance entitled "*Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies*" (Drug-Eluting Stent Guidance) as a guideline for the testing performed on the subject device. The testing was conducted to ensure that the GT1 BVS System performs as intended. The following tests were performed on the GT1 BVS System and the results were submitted for FDA review:

<u>Delivery System:</u>

Testing conducted using the GT1 BVS System is indicated by *italicized text*. All other testing was conducted using BVS systems that included the IDE delivery system.

- Dimensional Verification
  - Minimum Balloon Working Length
  - Guidewire Lumen Dimensions
  - *Tip Entry OD*
  - *Tip Length*
  - *Mid-Catheter Junction (Notch) OD*
  - *Total Catheter Length*
  - *Distal Catheter Length*
  - *Distal Shaft OD*
  - *Proximal Shaft OD*
- Balloon Shoulder to Marker (Proximal and Distal)
- *Proximal Shaft Marker Locations: Femoral*
- *Proximal Shaft Marker Locations: Brachial*
- Balloon Rated Burst Pressure/Maximum Labeled Compliance Pressure
- Balloon Fatigue Resistance

- Balloon Compliance (Stent Diameter vs. Balloon Pressure)
- *Balloon Inflation and Deflation*
- Inner Member Lumen Collapse
- *Catheter Preparation*
- *Catheter Body and Proximal Adaption Pressure Integrity*
- Catheter Bond Strength
    - *Proximal Balloon Seal Tensile*
    - *Notch Seal/Outer Member to Hypotube Tensile*
    - *Soft Tip Tensile*
    - *Proximal Adaption Tensile*
- *Torque Strength*
- *Flexibility and Kink Test*
- *Hydrophilic Coating (Dry Adhesion)*
- *Hydrophilic Coating (Coating Coefficient of Friction)*
- *Hydrophilic Coating Integrity (Visual Inspection)*
- *Tracking Particulate Count*
- *Tracking Particulate Count – Overlap*
- *Delivery, Deployment and Retraction*

Scaffold Component

The testing conducted using the GT1 BVS System indicated by *italicized text*. All other testing was conducted using BVS systems that included the IDE delivery system.

- Dimensional Verification
    - Nominal Scaffold ID
    - Scaffold Dimensions
- Scaffold Markers (Marker Verification)
- Scaffold Placement (Visual Inspection)
- Percent Surface Area
- Maximum Crossing Profile Diameter
- Scaffold Dislodgement (Distal and Proximal)
- Pullback into Guiding Catheter
- Scaffold Percent Length Change (Foreshortening – Nominal and Post-dil)
- Recoil for Balloon Expandable Stents
- Stent Integrity
- Uniformity of Expansion (Nominal)
- Inner Scaffold Diameter Prior to Strut Fracture (Post-dilate to Fracture)
- Circumferential Radial Strength (Nominal and Post-dil)
- Radial Stiffness
- Longitudinal Scaffold Compression
- Mechanical Properties
- Stress /Strain Analysis
    - Acute Integrity Stress Analysis (Finite Element Analysis – FEA)
    - Fatigue Stress Analysis (FEA)
- Fatigue Analysis
    - Structural Fatigue Testing

    - Embolic Fatigue and Coating Fatigue
- Accelerated Durability Testing
- Particulate Evaluation
- Magnetic Resonance Imaging (MRI) Safety and Compatibility
- *Radiopacity*
- *In vitro* scaffold degradation
- Evaluation of intermediate degradation products

Drug-Eluting Coating Testing

- Coating Characterization
    - Coating Microstructure
    - Coating Thickness
    - Drug Content Along the Length of the Stent
- Coating Integrity
- Beaker Particulate Count
- Particulate Matter Characterization
    - Acute Particulate Chemical Characterization
    - Embolic Fatigue Particulate Chemical Characterization
- *In vitro* Coating Degradation

The review team has completed its review of the device non-clinical performance testing, including the drug-eluting coating, and has no outstanding concerns related to the baseline characterization or product stability.

5.2 Chemistry, Manufacturing and Controls (CMC) Testing

The drug substance, everolimus, is purchased from a drug manufacturer (Novartis – Basel, Switzerland). CMC information describing the manufacture and controls of the everolimus drug substance is incorporated in the Absorb GT1 BVS System PMA by authorized reference to the Drug Master File (DMF). The everolimus drug substance meets the quality specifications that were developed based on the US Pharmacopoeia (USP) and European Pharmacopoeia (EP). The CMC information for the drug substance was reviewed and found to be acceptable.

For the finished product, the sponsor provided the details of the manufacturing process, the quantitative composition of the product, controls for the everolimus drug substance used in the manufacture of the GT1 BVS, including the analytical test methods and supporting validation data and stability data. The sponsor also proposed a finished product specification, including the analytical procedures and supporting validation data. There are no outstanding CMC issues related to these specifications.

5.3 Biocompatibility Testing

Abbott Vascular identified all material components of the GT1 BVS System and used the guidance provided in "*Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*" *Draft Guidance for Industry and Food and Drug Administration Staff*" and "*ISO 10993-1:2009 Biological Evaluation of Medical Devices – Part 1: Evaluation and testing within a risk management process*" to determine which tests were

necessary for establishing the safety profile of the materials used in the GT1 BVS System on both the ODS and the GT1 BVS (both with and without the drug coating). The components were separately tested so as to attribute the observed response to the specific component of the device. Additionally, the GT1 BVS was tested without the drug coating because the inclusion of everolimus, a known cytostatic API, may impact the results of the biocompatibility assessment. The following biocompatibility tests were performed and the results were submitted for FDA review:

Delivery System without Drug-Coated Scaffold

- Cytotoxicity (MEM Elution)
- Sensitization (Guinea Pig Maximization)
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Hemocompatibility
    - Hemolysis (Direct and Indirect)
    - Complement Activation Assay
        - C3a
        - SC5b-9
    - Coagulation
        - PT
        - PTT
- Material Mediated Pyrogenicity

Drug-Coated Scaffold

- Cytotoxicity (MEM Elution Method)
- Sensitization (Guinea Pig Maximization)
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Genotoxicity
    - Gene Mutation in Bacteria (AMES)
    - Gene Mutation in Mammalian Cells (Chromosomal Aberration)
    - Clastogenicity in Mammalian Cells
    - Mammalian Erythrocyte Micronucleus Test
- Carcinogenicity and Chronic Toxicity
- Reproductive/Developmental Toxicity
- Implantation (90-Day Intramuscular or the clinically-relevant Porcine Coronary Model)
- Hemocompatibility
    - Hemolysis (Direct and Indirect)
    - Complement Activation Assay
        - C3a
        - SC5b-9
    - Coagulation
        - PT
        - PTT
- Material Mediated Pyrogenicity
- 90-Day Implantation

- Sub-Chronic Toxicity

Polymer-Only Scaffold

- Cytotoxicity (MEM Elution Method)
- Sensitization (Guinea Pig Maximization)
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Genotoxicity
    - Gene Mutation in Bacteria (AMES)
    - Gene Mutation in Mammalian Cells (Chromosomal Aberration)
    - Clastogenicity in Mammalian Cells
    - Mammalian Erythrocyte Micronucleus Test
- Carcinogenicity and Chronic Toxicity
- Reproductive/Developmental Toxicity
- Implantation (90-Day Intramuscular or the clinically-relevant Porcine Coronary Model)
- Hemocompatibility
    - Hemolysis (Direct and Indirect)
    - Complement Activation Assay
        - C3a
        - SC5b-9
    - Coagulation
        - PT
        - PTT
    - Material Mediated Pyrogenicity

Based on the information provided by the sponsor as outlined above, FDA concluded that the Absorb BVS demonstrated acceptable biocompatibility.

5.4 Non-clinical *In Vivo* Animal Studies

Abbott Vascular conducted a comprehensive series of animal studies to demonstrate *in vivo* safety and to assess the *in vivo* pharmacokinetics and degradation profiles of the GT1 BVS System. All animal studies were carried out in a porcine (cross-bred farm swine and Yucatan mini swine) non-atherosclerotic model for durations of up to 48 months. A total of 258 swine underwent experimental procedures across all animal studies.

5.4.1 Non-clinical Safety Summary

For the GLP safety studies, the evaluation included assessments of systemic, imaging (angiographic, IVUS and OCT methods) and vascular response (utilizing histology, histomorphometry, and scanning electron microscopy) endpoints. The studies were designed to assess the *in vivo* response through each performance phase of the scaffold: revascularization (through day 180), restoration (6 – 18 months) and resorption (18 – 36 months). The BVS was studied in both single and overlapped configurations.

The *in vivo* animal studies demonstrated generally comparable nonclinical safety outcomes of the BVS System compared to the XIENCE stent in the porcine model. Arteries implanted with the

BVS remained patent, and the implants were incorporated within a smooth muscle cell-rich neointima. Inflammation scores remained within acceptable limits at all time points. There was no evidence of local vascular toxicity or significant negative remodeling. Complete endothelialization confirmed by scanning electron microscopy was achieved within 90 days of implantation.

Scaffold resorption, as indicated by *in vivo* mass loss, progressed from <10% at 12 months to complete resorption by approximately 36 months.

5.4.2 Non-clinical Pharmacokinetics (Systemic and Arterial Tissue) Summary

The GLP PK Studies demonstrated that 78-79% of the everolimus was eluted at 28 days and 96% was eluted at 90 days. Therapeutic concentrations of everolimus were maintained in target arteries for at least 28 days following implantation while a systemic safety profile was demonstrated in those studies.

Whole blood samples were collected at each sampling time point. In addition to whole blood samples, the implanted arteries and a sampling of myocardium (subjacent and distal to implanted artery), left lung, liver, spleen and kidneys were collected at termination and analyzed.

Following treatment, systemic levels peaked within 15 minutes (C_{max} = 2.83 ng/mL) and then declined rapidly (C = 0.28 ng/ml, 24 hours). As expected, everolimus concentrations were highest in the implanted artery segment (C_{max} = 22.70 ng/mg, 3 hours; 2.07 ng/mg, 28 days), as compared to other organs such as the myocardium (less than limit of quantitation beyond 14 days) and left lung (less than limit of quantitation by 1 day), which persisted for every evaluation time point. The concentration was below the limit of quantitation for the spleen, the liver and the kidneys for every evaluation time point.

5.4.3 Clinical Pharmacokinetics Summary

The ABSORB III-PK substudy is a prospective, open-label, unblinded sub-study to determine the pharmacokinetics of everolimus delivered by the Absorb BVS in a separate and non-randomized group of ABSORB III subjects who only receive Absorb BVS with a maximum of two *de novo* native coronary artery lesions. The PK substudy enrolled 12 subjects at 2 clinical sites beginning in June 2014. The study subjects received either one (n = 8) or two (n = 4) Absorb BVS with the diameters of 2.5, 3.0 and 3.5 mm and lengths of 8, 12, 18, and 28 mm. The total everolimus dose ranged from 181 to 443 μg. The maximum observed everolimus concentration (C_{max}) increased with increasing dose and ranged from 1.085 – 4.460 ng/mL across the dosage range studied. Similarly, individual AUC_{24h} (ranging from 12.09 – 44.22 ng*h/mL), AUC_{last} (ranging from 25.37 – 104.6 ng*h/mL) and $AUC_{0-\infty}$ (ranging from 33.15 – 120.8 ng*h/mL) increased proportionally with dose. These results are consistent with those found with the XIENCE V stent, where everolimus blood concentrations increased rapidly after implantation and then declined exponentially over a period of 7 days.

See Appendix 1 for further details.

5.4.4 *In vivo* Polymer Degradation Study

In vivo molecular weight degradation of the GT1 BVS was evaluated by gel permeation

chromatography (GPC) following implantation in naïve porcine coronary arteries. These studies indicated that the polymer was completely resorbed within approximately 36 months, which is consistent with *in vitro* findings.

5.5 Toxicology

Toxicology information on everolimus was incorporated by reference to the manufacturer's drug master file (DMF). FDA has reviewed this information, and there are no remaining concerns. Based on known risks associated with everolimus use (as described in the DMF), the labeling proposed by the applicant included the following sections:

- Immune Suppression Potential
- Lipid Elevation Potential
- Pregnancy
- Lactation

The Instructions for Use make the following statements:

- Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.
- Oral administration of everolimus in combination with cyclosporine has been associated with increased serum cholesterol and triglycerides.
- The Absorb GT1 BVS should be used in pregnant women only if potential benefits outweigh potential risks.
- The safety of the Absorb GT1 BVS has not been evaluated in males intending to father children.
- Prior to Absorb GT1 BVS implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

5.6 Sterilization

The GT1 BVS System is provided sterile. After reviewing the information submitted by the sponsor, the review team has concluded that under the stated exposure conditions, the electron beam cycle will render the GT1 BVS System sterile at a sterility assurance level of 10^{-6}. An SAL of 10^{-6} indicates that there will be no more than one survivor in one million sterilized products. Packaging studies were performed to demonstrate that the current packaging configuration will maintain a sterile barrier to support the forthcoming shelf-life claim.

5.7 Manufacturing

FDA has reviewed the manufacturing information. All of the manufacturing facilities have been inspected and were found to be in compliance

5.8 Non-Clinical Studies Summary and Clinical Correlation

The sponsor presented a comprehensive non-clinical package evaluating the performance of the BVS on the bench as well as in a healthy animal model. Based on the non-clinical information presented, the BVS undergoes hydrolytic degradation and is absorbed in an *in vivo* model, where the scaffold is fully degraded by approximately 36 months..

In vivo animal studies demonstrated complete scaffold degradation by approximately 36 months. Struts were eventually replaced by connective tissue confluent with the surrounding arterial wall. There was an early and late bi-modal pattern of tissue inflammation, but inflammation scores remained within acceptable limits. There was no evidence of local vascular toxicity, significant negative remodeling or unacceptable rates of unintended scaffold fracture or strut mal-apposition. The BVS was covered by a smooth muscle cell-rich neointima with near complete (> 90%, 28 days) to complete (90 days) endothelialization.

Intracoronary imaging studies including IVUS and OCT were performed on subjects enrolled in the ABSORB Cohort B study (to 5 years) and were consistent with the *in vivo* animal studies. In stent late lumen loss in ABSORB Japan at 13 months, and in ABSORB Cohort B at various time points out to 5 years, was generally similar to that observed in XIENCE stents. Rates of unintended BVS fracture, strut mal-apposition, and adverse positive or negative remodeling were low.

6 CLINICAL STUDIES

The principal safety and effectiveness information for the Absorb GT1 BVS System is derived from the ABSORB III Randomized Clinical Trial (RCT).

6.1 ABSORB III Trial

Objective: To evaluate the safety and effectiveness of the Absorb BVS System compared to XIENCE in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels.

An outline of the ABSORB III trial is shown in Figure 6.1-1.

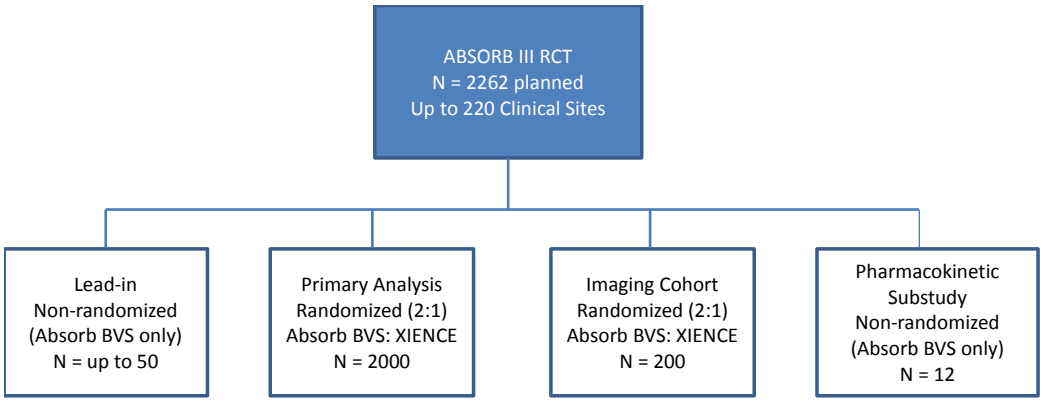


Figure 6.1-1. Absorb III Overall Design

- **Lead-in Group:** A single-arm, open-label group to evaluate the ABSORB training program for US physicians. Enrollment of lead-in subjects began on December 28, 2012 and was completed on April 1, 2013 (total of 24 subjects). See Appendix 1.
- **Primary Analysis Group:** A prospective, randomized (2:1 Absorb to XIENCE), single-blinded, multi-center trial. The first randomized subject was enrolled on March 22, 2013, and the last subject was enrolled on April 3, 2014 (total of 2008 subjects). The last 1-year follow-up visit for primary analysis group subjects occurred on April 2, 2015. The database

was locked for the 1-year analysis on April 2, 2015.

- **Imaging Cohort:** A prospective, randomized (2:1 Absorb to XIENCE), single-blinded, multi-center sub-study to evaluate long-term vascular function and patency of the BVS vs. XIENCE-treated arteries. The Imaging Cohort subjects are separate from the primary analysis Group subjects. The first Imaging Cohort subject was enrolled on April 22, 2014, and the last subject was enrolled on September 28, 2015 (total of 186 subjects). Imaging data will be pooled with the ABSORB Japan RCT to evaluate: (1) in-stent/scaffold mean lumen area change from post-procedure to 3 years by IVUS; and (2) angiographic in-stent/scaffold mean lumen diameter change between pre- and post-nitrate infusion at 3 years. The Imaging Cohort study is ongoing, and no data were provided by the sponsor or reviewed by FDA.
- **Pharmacokinetic (PK) Group:** A prospective, open-label, unblinded sub-study to determine the pharmacokinetic profile of everolimus delivered by the BVS. The first PK subject was enrolled on June 2, 2014 and the last subject was enrolled on September 17, 2014 (total of 12 subjects). See Appendix 1.

Data from the Lead-in group, Imaging Cohort, and PK Group do not contribute to the ABSORB III primary endpoint analysis.

6.1.1 ABSORB III: Primary Analysis Group

Design: A prospective, randomized, single-blinded, multi-center trial

Test Device: Absorb BVS

Control Device: XIENCE stent

Randomization Scheme: Subjects were randomized 2:1 to the BVS or XIENCE group, stratified by diabetes mellitus status (diabetic vs. non-diabetic), intended dual vessel treatment (single target lesion vs. dual target lesion treatment), and site.

Blinding: The trial is single-blinded with subjects blinded to their treatment assignment.

Primary Endpoint*:* Target lesion failure (TLF) at 1 year. TLF is defined as the composite of: cardiac death, myocardial infarction (MI) attributable to target vessel (target vessel MI, TV-MI), or ischemia-driven target lesion revascularization (ID-TLR).

Secondary Endpoints with Pre-specified Hypothesis Tests

- Angina at 1 year
- All revascularizations at 1 year
- Ischemia-driven target vessel revascularization (ID-TVR) at 1 year

Additional Secondary Endpoints

- Death (cardiac, vascular, non-vascular)
- Target vessel MI (TV-MI) and non-target vessel MI
- Ischemia-driven or non-ischemia-driven TLR
- Ischemia-driven or non-ischemia-driven TVR
- Death and all MI

- Cardiac death and all MI
- Cardiac death, all MI, and ID-TLR (MACE)
- Target Vessel Failure (TVF): Cardiac death, target vessel MI, ID-TLR, ID-TVR (non-target lesion)
- Death, all MI, all revascularization
- Scaffold/stent thrombosis (per ARC definition):
    - Timing (acute, sub-acute, late, and very late)
    - Evidence (definite and probable)

Key Clinical Inclusion Criteria

- Evidence of myocardial ischemia (*e.g.*, stable or unstable angina, silent ischemia)
- One (target) or two *de novo* lesions (two target lesions or one target and one non-target) each in a different epicardial vessel
- Target lesion(s) must be in a native coronary artery with reference vessel diameter (RVD) by visual estimation of ≥2.5 mm and ≤3.75 mm by visual estimate [use of vessel sizing methods such as quantitative coronary angiography (QCA), IVUS, or OCT were optional]
- Lesion(s) must be located in a native coronary artery ≤24 mm in length by visual estimation
- Visually estimated diameter stenosis of ≥50% and <100% with a TIMI flow of ≥1

Key Exclusion Criteria

- Acute MI within 72 hours of the index procedure
- LVEF <30%
- Subject receiving chronic anticoagulation therapy
- Subject with known renal insufficiency with an estimated GFR <30 ml/min/1.73m^2 or dialysis at the time of screening
- Subject requiring at least two lesion treatment and more suitable for staged PCI
- Heavily calcified lesion or lesions preventing complete balloon pre-dilatation
- Moderate or heavy calcification, tortuosity or other conditions are present proximal or within the target segment, reducing the likelihood that the Absorb BVS or XIENCE can be either delivered to or expanded at the lesion.
- Extreme angulation (≥90°) proximal to or within the target lesion
- Excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion
- Lesion located within or distal to a diseased arterial graft or SVG
- Aorto-ostial lesion (within 3 mm of the aorta junction)
- Lesion located in the left main
- Lesion located within 2 mm of the origin of the LAD or LCX.
- Lesion involving a bifurcation with a:
    1. side branch ≥ 2 mm in diameter, or
    2. side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or
    3. side branch requiring dilatation
- Target vessel contains thrombus

PCI Treatment

- Successful pre-dilation was mandatory, defined as
    - Residual percent diameter stenosis (%DS) <40%

  - TIMI-3 flow
  - Lesion length (including any edge dissection) <24 mm
  - No other significant angiographic or clinical complications, such as side branch occlusion or distal embolization, chest pain >5 minutes, or ST segment ECG changes
- Vessel size ≥2.5 mm and ≤3.75 mm assessed by visual estimation following intracoronary nitroglycerine with optional use of online QCA, IVUS or OCT
- Post dilation optional utilizing a noncompliant balloon with a caution not to dilate >0.5 mm beyond the nominal BVS diameter.

Peri-procedural Cardiac Biomarker Measurements

- Pre-procedure CK and CK-MB
- First post-procedure CK and CK-MB at 6 to 12 hours post-procedure
- Second post-procedure CK and CK-MB at 18-24 hours post-procedure, or at the time of discharge as long as discharge is at or after 16 hours post-procedure

Antiplatelet Therapy

- ***Pre-procedure***
  - Loading dose of ≥300 mg of aspirin within 24 hours, but no later than 1 hour prior to the index procedure
  - Loading dose of an ADP antagonist (clopidogrel, prasugrel or ticagrelor) within 24 hours prior to the index procedure (preferred) or no longer than 1 hour post-procedure.
- ***Post-procedure***
  - 75 mg of clopidogrel daily, 5 or 10 mg of prasugrel daily (10 mg preferred in most patients), or 90 mg twice daily of ticagrelor for a minimum of 12 months following the index procedure
  - ≥75 to ≤100 mg of aspirin daily through 5 years follow-up during the study and then indefinitely

Follow-up*:* Clinical follow-up at the following time points post-index procedure:

- 30 ± 7 days
- 180 ± 28 days
- 1 year ± 28 days (office visit and ECG required)
- Annually ±28 days for years 2 to 5

Statistical Analysis Plan

Analysis populations

- ***Intent-To-Treat (ITT) Population:*** Defined as subjects registered in the study at the point of randomization, regardless of the treatment actually received. Subjects are analyzed in the treatment group to which they were randomized. The ITT population was pre-specified in the study protocol (Version 13.0).
- ***Per-Treatment-Evaluable (PTE) Population:*** Defined as subjects who have received only study device(s) (Absorb BVS or XIENCE) at the target lesion. The PTE population is analyzed based on the treatment actually received, and excludes subjects with protocol deviations that are described in Appendix 8. The PTE population was pre-specified in the study protocol (Version 13.0).

- ***As-Treated (AT) population:*** Treatment group assignment in the AT population was based on the treatment (BVS or XIENCE) actually received. Subjects who received both BVS and XIENCE treatment in separate target lesions were included in the treatment group to which they were randomized. Subjects who received both BVS and XIENCE treatment in the same target lesion and those who received no study device were excluded from the AT population. The AT population was not pre-specified in the study protocol (Version 13.0).

Primary endpoint hypotheses and sample size: The null and alternative hypotheses for non-inferiority test of the primary 1-year TLF endpoint are as follows:

$$H_0: TLF_{BVS} - TLF_{XIENCE} \geq \Delta$$
$$H_1: TLF_{BVS} - TLF_{XIENCE} < \Delta,$$

where TLF_{BVS} and TLF_{XIENCE} are the 1-year TLF rates in the Absorb BVS and XIENCE groups, respectively. Δ is the non-inferiority (NI) margin of 4.5%. The hypothesis test was planned to be conducted at a one-sided level of significance 0.025. The sample size calculation was based on the following assumptions:

- One-sided $\alpha = 0.025$
- The true 1-year TLF rate was assumed to be 7.0% for both the BVS and XIENCE groups
- Non-inferiority margin (Δ) = 4.5%
- A 5% lost to follow-up rate at 1 year

An effective sample size of 1,900 subjects (1,267 for the Absorb BVS arm and 633 for the XIENCE arm) provide approximately 96% power.

Secondary endpoints with pre-specified hypothesis tests: If the non-inferiority test of the primary endpoint TLF at 1 year was passed, superiority tests of the three secondary endpoints with pre-specified hypothesis tests (angina at 1 year, all revascularizations at 1 year, and ischemia-driven target vessel revascularization at 1 year) were to be performed based on a pre-specified testing sequence (Figure 6.1-2) such that as soon as a null hypothesis was not rejected, testing stopped and the null hypotheses of subsequent tests were not rejected.

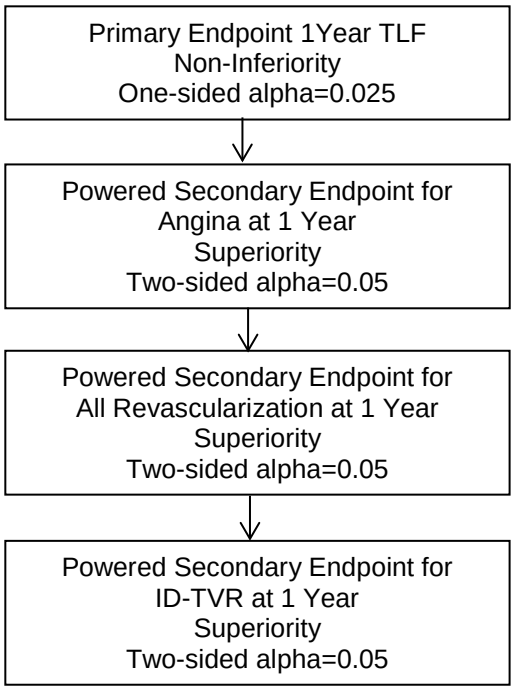


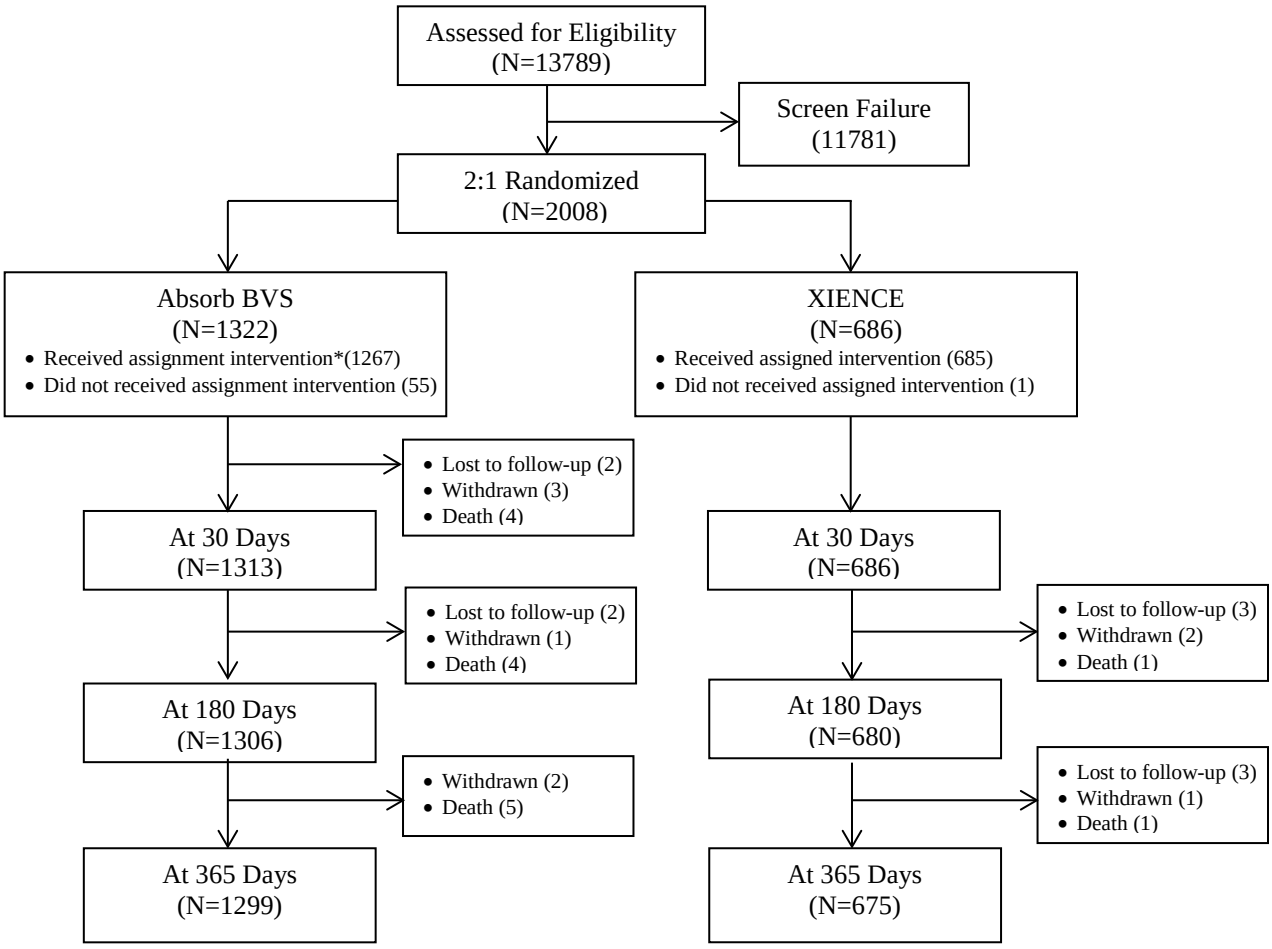
Figure 6.1-2. Clinical Study Testing Flow (Primary Analysis Group)

6.1.2 ABSORB III Trial Results

Patient Accountability

- A total of 13,789 subjects were screened for eligibility in ABSORB III, of which 2008 subjects were randomized at 193 study sites between March 22, 2013 and April 3, 2014
    - 1322 BVS subjects (1385 lesions treated)
    - 686 XIENCE subjects (713 lesions treated)
- Early subject termination through 365 days (due to loss to follow-up, withdrawal, or death) was as follows:
    - BVS: 23 of 1322 (1.7%) subjects
    - XIENCE: 11 of 686 (1.6%) subjects

All available subjects have completed their 1-year follow-up, and follow-up through 5 years is ongoing (Figure 6.1-3).



***** Includes 11 subjects who received assigned study device in one lesion but did not receive assigned study device in a second lesion.

Figure 6.1-3. Patient Accountability of the Primary Analysis Group

Study Population Demographics and Baseline Parameters

The key baseline demographic and clinical characteristics for the ITT population are shown in Table 6.1-1. There were no statistical differences in baseline features identified between treatment groups.

Table 6.1-1. Study Population Demographics and Baseline Parameters – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
Age (year)	63.5 ± 10.6 (1322)	63.6 ± 10.3 (686)	-0.2 [-1.1, 0.8]
Male Subjects	70.7% (934/1322)	70.1% (481/686)	0.53% [-3.62%, 4.80%]
Body Mass Index (kg/m^2)	30.58 ± 6.22 (1322)	30.47 ± 6.26 (686)	0.11 [-0.47, 0.69]
Current Tobacco Use	21.3% (281/1322)	20.7% (142/686)	0.56% [-3.28%, 4.22%]
Any Diabetes Mellitus (DM)	31.5% (416/1320)	32.7% (224/686)	-1.14% [-5.49%, 3.12%]
DM req. Med.	28.2% (372/1320)	28.4% (195/686)	-0.24% [-4.46%, 3.85%]
DM req. Insulin	10.5% (138/1320)	11.2% (77/686)	-0.77% [-3.77%, 2.01%]
HbA1c (%) (All Diabetes Mellitus)	7.56 ± 1.76 (389)	7.78 ± 2.06 (209)	-0.22 [-0.55, 0.11]
Hypertension req. Med.	81.0% (1071/1322)	80.6% (553/686)	0.40% [-3.15%, 4.12%]
Dyslipidemia req. Med.	76.3% (1009/1322)	77.7% (533/686)	-1.37% [-5.16%, 2.57%]
Prior Coronary Intervention	38.7% (512/1322)	38.0% (260/684)	0.72% [-3.79%, 5.16%]
Prior MI	21.5% (282/1311)	22.0% (150/681)	-0.52% [-4.42%, 3.23%]
Cardiac Status			
AMI	2.8% (37/1321)	2.6% (18/686)	0.18% [-1.49%, 1.59%]
Unstable Angina	26.9% (355/1321)	24.5% (168/686)	2.38% [-1.70%, 6.31%]
Stable Angina	57.3% (757/1321)	60.8% (417/686)	-3.48% [-7.96%, 1.07%]
Silent Ischemia	10.0% (132/1321)	10.2% (70/686)	-0.21% [-3.12%, 2.47%]
No Current Evidence of Ischemia	2.1% (28/1321)	1.3% (9/686)	0.81% [-0.52%, 1.92%]
Single diseased artery	69.5% (919/1322)	67.2% (461/686)	2.31% [-1.93%, 6.65%]
Two diseased arteries	24.3% (321/1322)	26.4% (181/686)	-2.10% [-6.19%, 1.85%]
Three or more diseased arteries	6.2% (82/1322)	6.4% (44/686)	-0.21% [-2.61%, 1.94%]

[1]Without multiplicity adjustment.

Baseline Lesion Characteristics and Pre-Procedure QCA Results

Key baseline lesion morphology and quantitative coronary angiography (QCA) results for the ITT population, are shown in Table 6.1-2. Lesion characteristics were balanced between the treatment groups except for the proportion of LCX/ramus artery treatment (lower in the BVS group), and mean lesion length was shorter in the BVS group vs. the XIENCE group (12.60 ± 5.41 mm and 13.12 ± 5.82 mm, respectively).

Table 6.1-2. Baseline Lesion Characteristics and QCA by Angiographic Core Lab – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	Absorb BVS (N=1322) (L=1385)	XIENCE (N=686) (L=713)	Difference [95% CI][1]
Target Vessels			
# Target Lesions	1.0 ± 0.2 (1321)	1.0 ± 0.2 (686)	0.0 [-0.0, 0.0]
LAD	44.5% (617/1385)	42.2% (301/713)	2.33% [-2.15%, 6.77%]
LCX/Ramus	26.2% (363/1385)	30.6% (218/713)	-4.37% [-8.51%, -0.32%]
RCA	29.2% (404/1385)	27.2% (194/713)	1.96% [-2.15%, 5.94%]
LMCA	0.1% (1/1385)	0.0% (0/713)	0.07% [-0.47%, 0.41%]
Lesion Morphology			
Type B2/C	68.7% (949/1381)	72.5% (513/708)	-3.74% [-7.77%, 0.42%]
Calcification (moderate/severe)	33.1% (457/1379)	32.1% (227/708)	1.08% [-3.21%, 5.26%]
Bifurcations	37.0% (510/1380)	37.4% (264/706)	-0.44% [-4.85%, 3.90%]
Tortuosity (moderate/severe)	2.9% (40/1380)	4.0% (28/708)	-1.06% [-2.92%, 0.52%]
Eccentric Lesion	75.8% (1046/1380)	75.7% (536/708)	0.09% [-3.72%, 4.04%]
Pre-Procedure Measurement by QCA			
Lesion Length (mm)	12.60 ± 5.41 (1378)	13.12 ± 5.82 (708)	-0.52 [-1.04, -0.01]
RVD (mm)	2.67 ± 0.45 (1380)	2.65 ± 0.46 (708)	0.02 [-0.02, 0.06]
MLD (mm)	0.92 ± 0.37 (1380)	0.90 ± 0.34 (708)	0.03 [-0.01, 0.06]
%DS	65.25 ± 12.48 (1380)	65.90 ± 11.66 (708)	-0.65 [-1.74, 0.43]

[1]Without multiplicity adjustment. Note: L=Number of lesions; N=Number of subjects.

Pre-Dilatation and Post-Device (Scaffold or Stent) Implantation QCA Results

QCA measurements following pre-dilatation ("post pre-dilatation") and post-device (scaffold or stent) implantation are shown in Table 6.1-3**.** Post pre-dilatation, the percent diameter stenosis (%DS) was slightly lower in the BVS group (41.41 ± 14.55%) vs. XIENCE (42.84 ± 14.02%).

After scaffold/stent implantation and post-dilatation (if used), reference vessel diameter (RVD), and *in-segment* minimal lumen diameter (MLD), %DS, and acute gain were similar between treatment groups. However, the observed *in-device* %DS was greater in the BVS group (11.62 ± 8.77%) vs. XIENCE (6.41 ± 8.91 %). The observed *in-device* MLD and acute gain in the BVS group (2.37 ± 0.40 mm and 1.45 ± 0.45 mm, respectively) were smaller than in the XIENCE group (2.49 ± 0.40 mm and 1.59 ± 0.44 mm, respectively). The total scaffold or stent slightly shorter in the BVS group vs. the XIENCE group (18.02 mm vs. 19.13 mm, respectively).

Table 6.1-3. Procedural QCA Results by Angiographic Core Lab – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	Absorb BVS (N=1322) (L=1385)	XIENCE (N=686) (L=713)	Difference [95% CI][1]
Post Pre-Dilatation Measurement by QCA			
RVD (mm)	2.67 ± 0.46 (1303)	2.66 ± 0.46 (648)	0.01 [-0.03, 0.05]
MLD (mm)	1.56 ± 0.45 (1303)	1.51 ± 0.43 (648)	0.04 [0.00, 0.09]
%DS	41.41 ± 14.55 (1303)	42.84 ± 14.02 (648)	-1.43 [-2.77, -0.09]
Post-Procedure Measurement by QCA			
RVD (mm)	2.70 ± 0.45 (1374)	2.68 ± 0.47 (706)	0.02 [-0.02, 0.06]
In-Segment MLD (mm)	2.15 ± 0.41 (1374)	2.14 ± 0.43 (706)	0.01 [-0.03, 0.05]
In-Segment %DS	20.04 ± 7.94 (1374)	19.82 ± 8.20 (706)	0.23 [-0.51, 0.96]
In-Segment Acute Gain (mm)	1.23 ± 0.46 (1373)	1.24 ± 0.44 (706)	-0.01 [-0.05, 0.03]
In-Device MLD (mm)	2.37 ± 0.40 (1373)	2.49 ± 0.40 (706)	-0.12 [-0.15, -0.08]
In-Device %DS	11.62 ± 8.77 (1369)	6.41 ± 8.91 (702)	5.21 [4.40, 6.02]
In-Device Acute Gain (mm)	1.45 ± 0.45 (1372)	1.59 ± 0.44 (706)	-0.14 [-0.18, -0.10]
Total Stent/Scaffold Length (mm)	18.02 ± 6.43 (1373)	19.13 ± 7.62 (706)	-1.11 [-1.77, -0.45]

[1]Without multiplicity adjustment. Note: L=Number of lesions; N=Number of subjects.

Use of Post-Dilatation

Post-dilatation was performed significantly more frequently in BVS-treated lesions (64.8%; 898 of 1385) compared to the XIENCE-treated lesions (49.9%; 356 of 713), a difference of 14.91% (95% CI of 10.45% to 19.32%).

6.1.2.1 Primary Endpoint Results

The primary endpoint for the ABSORB III randomized trial was target lesion failure (TLF) at 12 months, which is a composite of safety (cardiac death and target vessel MI) and effectiveness (ischemia-driven target lesion revascularization, ID-TLR) outcomes.

For the ITT population, the 1-year TLF rates in the BVS and XIENCE groups were 7.8% (102/1313) and 6.1% (41/677), respectively (Table 6.1-4a). The difference in 1-year TLF rate between the two study groups was 1.71% with corresponding 95% confidence interval (CI) of (-0.51%, 3.93%), the upper bound of which was less than the pre-specified non-inferiority margin of 4.5%. Therefore, the non-inferiority endpoint for the BVS vs. XIENCE was met (p=0.0070).

Table 6.1-4a. ABSORB III Primary Endpoint Analysis (Primary Analysis Group, ITT Population, Per-Protocol MI Definition)

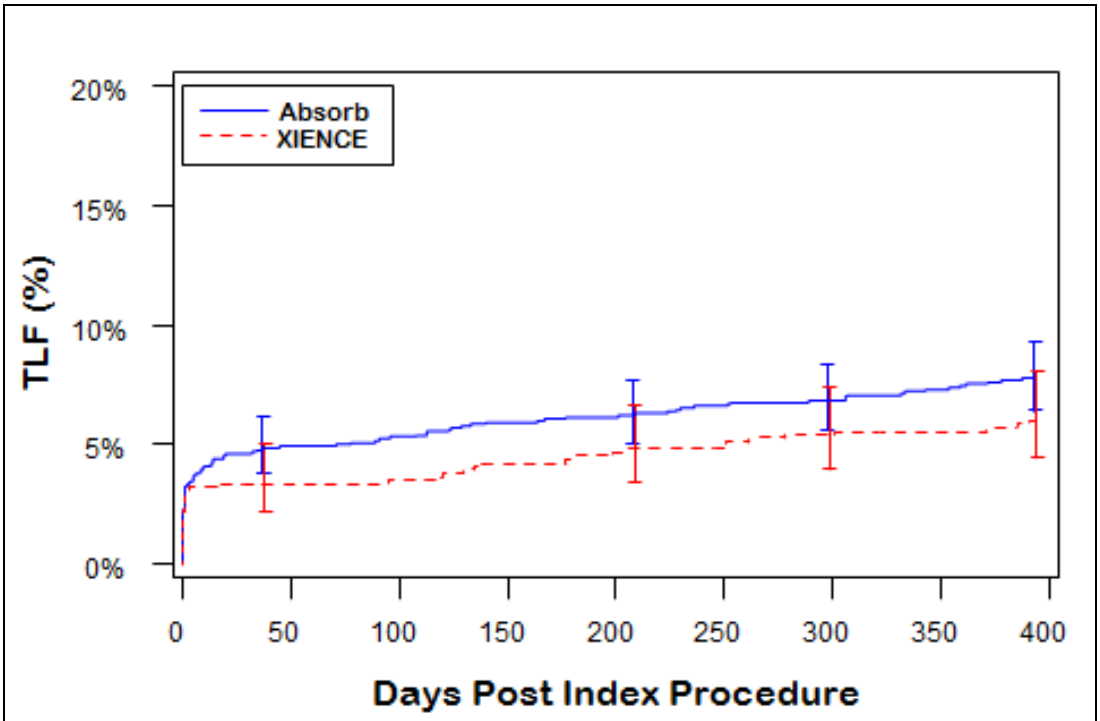
	BVS (N=1322)	XIENCE (N=686)	Difference (95% CI)	Non-Inferiority P-Value
1-Year TLF (Cardiac Death, Target Vessel MI, ID-TLR)	7.8% (102/1313)	6.1% (41/677)	1.71% (-0.51%, 3.93%)	0.0070
Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively). Note: 1-year timeframe includes a window of +/- 28 days.				

For the PTE population, the 1-year TLF rates in the BVS and XIENCE groups were 7.8% (91/1174) and 5.7% (38/670), respectively (Table 6.1-4b). The difference in 1-year TLF rate between the two study groups was 2.08% with corresponding 95% CI of (-0.19%, 4.35%), the upper bound of which was less than the pre-specified non-inferiority margin of 4.5%. Therefore, the non-inferiority endpoint for the BVS vs. XIENCE was met (p=0.0183).

Table 6.1-4b. ABSORB III Primary Endpoint Analysis (Primary Analysis Group, PTE Population, Per-Protocol MI Definition)

	BVS (N=1180)	XIENCE (N=679)	Difference (95% CI)	Non-Inferiority P-Value
1-Year TLF (Cardiac Death, Target Vessel MI, ID-TLR)	7.8% (91/1174)	5.7% (38/670)	2.08% (-0.19%, 4.35%)	0.0183
Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any DMR event (all death, all MI (regardless of MI definition), all revascularization, respectively). Note: 1-year timeframe includes a window of +/- 28 days.				

A Kaplan-Meier curve showing the cumulative incidence rates of TLF through 1 year is shown in Figure 6.1-4.



Time After Index Procedure (days)						
		0	**37**	**208**	**298**	**393**
BVS	**# At Risk**	1322	1252	1227	1217	1196
	# Events	30	64	82	90	102
	% Survived	97.7%	95.2%	93.8%	93.2%	92.3%
	% SEM	0.4%	0.6%	0.7%	0.7%	0.7%
XIENCE	**# At Risk**	686	660	647	642	634
	# Events	15	23	33	37	41
	% Survive	97.8%	96.6%	95.2%	94.6%	94.0%
	% SEM	0.6%	0.7%	0.8%	0.9%	0.9%

Note: p = 0.1498 for the Log-Rank test comparing the survival curves for TLF through 1 year between the two study groups. This test was not pre-specified in the study protocol and was not adjusted for multiplicity.

Figure 6.1-4. Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of TLF through 1 Year (Primary Analysis Group, ITT Population, Per-Protocol MI Definition)

Table 6.1-5 shows TLF and target vessel MI rates stratified by in-hospital events, events through 30 days following the index procedure, and events to 1 year.

Table 6.1-5. TLF, Cardiac Death and Target Vessel MI: In-Hospital, at 30 days and at 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
In-Hospital			
TLF	3.3% (43/1319)	3.1% (21/686)	0.20% [-1.58%, 1.72%]
Cardiac Death	0.1% (1/1319)	0.0% (0/686)	0.08% [-0.48%, 0.43%]
TV-MI	3.0% (39/1319)	2.9% (20/686)	0.04% [-1.69%, 1.51%]
ID-TLR	0.3% (4/1319)	0.6% (4/686)	-0.28% [-1.21%, 0.31%]
0 to 30 Days			
TLF	4.9% (64/1317)	3.4% (23/686)	1.51% [-0.42%, 3.21%]
Cardiac Death	0.3% (4/1317)	0.0% (0/686)	0.30% [-0.28%, 0.78%]
TV-MI	4.3% (56/1317)	3.2% (22/686)	1.05% [-0.82%, 2.68%]
ID-TLR	1.2% (16/1317)	0.7% (5/686)	0.49% [-0.59%, 1.34%]
0 to 1 Year			
TLF	7.8% (102/1313)	6.1% (41/677)	1.71% [-0.74%, 3.93%]
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.46% [-0.29%, 1.06%]
TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44% [-0.74%, 3.39%]
ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.54% [-1.14%, 1.96%]

[1] Without multiplicity adjustment.
Note: All component endpoints are evaluated on a non-hierarchical basis.
Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through a given time point without DMR (death, MI, or revascularization).

Target vessel MIs comprised the majority of events at all-time points following the index procedure.

6.1.2.2 Safety: Cardiac Death, Target Vessel MI and Scaffold/Stent Thrombosis

Non-hierarchical 1-year summary data for the safety components of the TLF primary endpoint (cardiac death and target vessel MI) and ARC definite plus probable stent thrombosis are shown in Table 6.1-6. Event rates were all numerically higher in the BVS group.

Table 6.1-6. Non-Hierarchical Safety Components of the Primary TLF Endpoint and Scaffold/Stent Thrombosis at 1 Year (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.46% [-0.29%, 1.06%]
TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44% [-0.74%, 3.39%]
ARC Definite + Probable Scaffold/Stent Thrombosis	1.54% (20/1301)	0.74% (5/675)	0.80% [-0.32%, 1.72%]

[1] Without multiplicity adjustment.

Cardiac Death

The rate and timing of the cardiac death events is shown in Table 6.1-7.

Table 6.1-7. Non-Hierarchical Cardiac Death Events through In-Hospital, at 30 days and at 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
In-Hospital	0.1% (1/1319)	0.0% (0/686)	0.08% [-0.48%, 0.43%]
0 to 30 Days	0.3% (4/1317)	0.0% (0/686)	0.30% [-0.28%, 0.78%]
0 to 180 Days	0.4% (5/1315)	0.1% (1/681)	0.23% [-0.48%, 0.75%]
Cumulative to 1-Year	0.6% (8/1313)	0.1% (1/677)	0.46% [-0.29%, 1.06%]

[1] Without multiplicity adjustment.

The cardiac death rate was numerically higher in the BVS group vs. XIENCE. Clinical details regarding the cardiac death events are as follows:

BVS

Four cardiac deaths occurred within 30 days following the index procedure. There were no reported procedural complications.

- 55-year old woman had a respiratory arrest on the day of the index procedure. A repeat cardiac catheterization demonstrated 2 patent BVS. On day 1, the troponin I level was elevated (with a normal CK and CK-MB). The subject developed anoxic encephalopathy and expired on day 13. The autopsy report was not available. The investigator assessed this event as possibly related to the study procedure, not related to the study device, and not caused by a malfunction of the study device.
- 89-year old man developed a sudden change in mental status followed by cardiac arrest (pulseless electrical activity) on Day 2. A repeat cardiac catheterization demonstrated a patent BVS. The subject expired on day 2. The death certificate and autopsy report were not available. The investigator assessed this event as not related to the study procedure, not related to the study device, and not caused by a malfunction of the study device.
- Two sudden deaths were adjudicated as probable stent thrombosis (on day 3 and day 13):
    - 59-year old man was found unresponsive on day 3. Autopsy findings were suggestive of recent thrombotic occlusion in the LAD (BVS-treated vessel).
    - 74-year old man expired at home on day 13. The autopsy report was not available. The investigator assessed this event as unknown relation to the study procedure, unknown relation to the study device, and not caused by a malfunction of the study device.

One cardiac death occurred between 30 days and 6 months following the index procedure. There were no reported procedural complications.

- 48-year old man presented on day 122 with unstable angina and negative cardiac biomarkers. The subject was discharged on medical therapy on Day 123 and was found unresponsive and pulseless on Day 124. The cause of death per the autopsy report was atherosclerotic and hypertensive cardiovascular disease. The investigator assessed this event as unknown relation to the study procedure, unknown relation to the study device, and not caused by a malfunction of the study device.

Three cardiac deaths occurred between 6 months and 1 year. There were no reported procedural complications.

- 87-year old man presented with a stroke on Day 204. There were multiple medical complications, and the subject sustained a cardiopulmonary arrest on Day 332. The autopsy

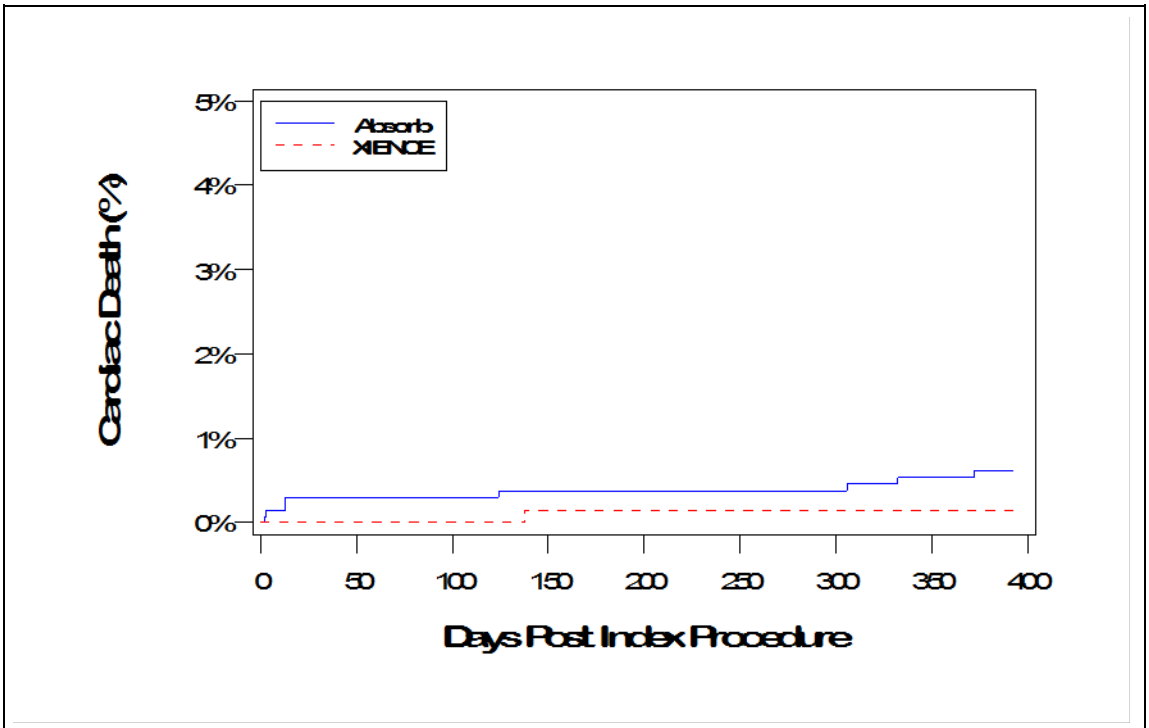
report was not available. The investigator assessed this event as not related to the study procedure, not related to the study device, and not caused by a malfunction of the study device.

- 60-year old man was found unresponsive on day 306. The subject was apneic, and the cardiac rhythm showed ventricular fibrillation and pulseless electrical activity. The autopsy report was not available. The investigator assessed this event as not related to the study procedure, unknown relation to the study device, and not caused by a malfunction of the study device.
- 73-year old man presented with unstable angina followed by a cardiac arrest on Day 372. The death certificate and autopsy report were not available. The investigator assessed this event as not related to the study procedure, possibly related to the study device, and possibly caused by a malfunction of the study device. The CEC additionally adjudicated a Type 3 MI that resulted in death with an undetermined relation to the target vessel.

XIENCE:
One cardiac death occurred between 30 days and 6 months following the index procedure. There were no reported procedural complications.

- 64 year old man expired on day 138. No details regarding this event are available. The cause of death per the death certificate was hypertensive and atherosclerotic cardiovascular disease. The autopsy report was not available. The investigator assessed this event as not related to the study procedure, unknown relation to the study device and not caused by a malfunction of the study device.

A Kaplan-Meier plot of cardiac death through 1-year is shown in Figure 6.1-5.



Time After Index Procedure (days)						
		0	**37**	**208**	**298**	**393**
BVS	**# At Risk**	1322	1310	1303	1301	1289
	# Events	0	4	5	5	8
	% Survived	100%	99.7%	99.6%	99.6%	99.4%
	% SEM	0.0%	0.2%	0.2%	0.2%	0.2%
XIENCE	**# At Risk**	686	683	679	678	674
	# Events	0	0	1	1	1
	% Survived	100%	100%	99.9%	99.9%	99.9%
	% SEM	0.0%	0.0%	0.1%	0.1%	0.1%

Note: p = 0.1435 for the Log-Rank test comparing the survival curves for cardiac death through 1 year between the two study groups. This test was not pre-specified in the study protocol and was not adjusted for multiplicity.

Figure 6.1-5. Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of Cardiac Death through 1 Year (ABSORB III Primary Analysis Group, ITT Population)

Target Vessel MI

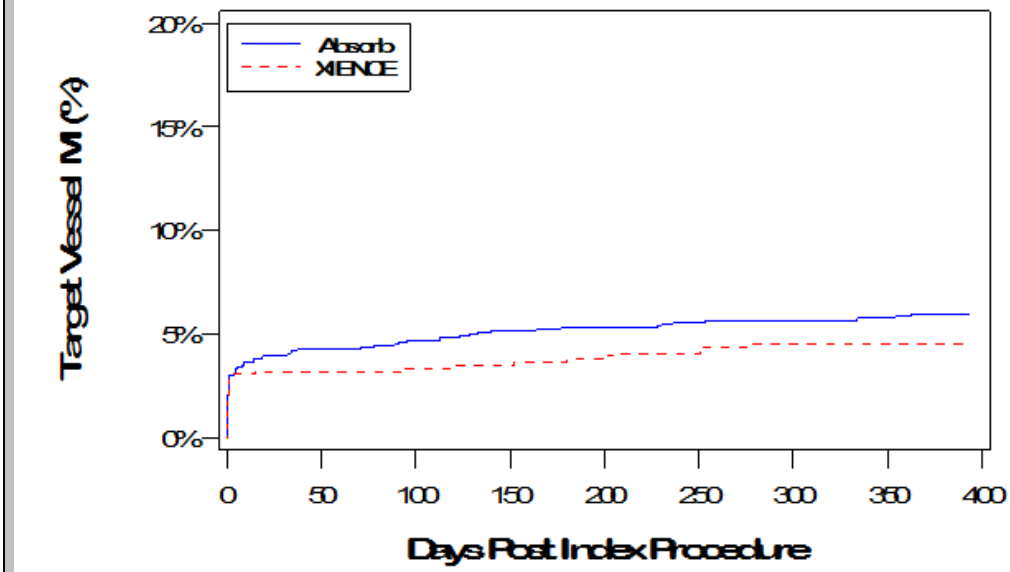
The rate and timing of the ABSORB III target vessel MI events are shown in Table 6.1-8.

Table 6.1-8. Non-Hierarchical Target Vessel MI Events: In-Hospital, at 30 days, at 180 Days and at 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	BVS(N=1322)	XIENCE(N=686)	Difference[95% CI][1]
In-Hospital (Peri-procedural)			
TV-MI	3.0% (39/1319)	2.9% (20/686)	0.04% [-1.69%, 1.51%]
Q-wave MI	0.1% (1/1319)	0.3% (2/686)	-0.22% [-0.98%, 0.20%]
Non-Q Wave MI	2.9% (38/1319)	2.6% (18/686)	0.26% [-1.42%, 1.68%]
0 to 30 Days			
TV-MI	4.3% (56/1317)	3.2% (22/686)	1.05% [-0.82%, 2.68%]
Q-wave MI	0.6% (8/1317)	0.3% (2/686)	0.32% [-0.51%, 0.94%]
Non-Q Wave MI	3.6% (48/1317)	2.9% (20/686)	0.73% [-1.05%, 2.27%]
0 to 180 days			
TV-MI	5.3% (70/1315)	4.1% (28/681)	1.21% [-0.86%, 3.05%]
Q-wave MI	0.7% (9/1315)	0.3% (2/681)	0.39% [-0.45%, 1.04%]
Non-Q Wave MI	4.6% (61/1315)	3.8% (26/681)	0.82% [-1.17%, 2.57%]
Cumulative to 1-Year			
TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44% [-0.74%, 3.39%]
Q-wave MI	0.7% (9/1313)	0.3% (2/677)	0.39% [-0.45%, 1.04%]
Non-Q Wave MI	5.3% (70/1313)	4.3% (29/677)	1.05% [-1.06%, 2.91%]

[1] Without multiplicity adjustment.

The difference in the rate of target vessel MIs between the BVS group and the XIENCE group increased numerically over the year following the index procedure, and the vast majority of events were non-Q wave MIs. A Kaplan-Meier plot of target vessel MI through 1-year is shown in Figure 6.1-6.



Time After Index Procedure (days)

		0	37	208	298	393
Absorb	# At Risk	1322	1256	1234	1228	1211
	# Events	27	56	70	74	79
	% Survived	98.0%	95.8%	94.7%	94.4%	94.0%
	% SEM	0.4%	0.6%	0.6%	0.6%	0.7%
XIENCE	# At Risk	686	661	651	647	643
	# Events	14	22	28	31	31
	% Survived	98.0%	96.8%	95.9%	95.5%	95.5%
	% SEM	0.5%	0.7%	0.8%	0.8%	0.8%
Test Between Groups		**Test**	**Chi-Square**	**DF**	**p-value**	

Note: p = 0.1735 for the Log-Rank test comparing the survival curves for target vessel MI through 1 year between the two study groups. This test was not pre-specified in the study protocol and was not adjusted for multiplicity.

Figure 6.1-6. Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of Target Vessel MI through 1 Year (ABSORB III Primary Analysis Group) (Intent-to-Treat Population) (Per Protocol MI Definition)

Peri-procedural MI

A peri-procedural CK-MB >5x the upper limits of normal was the per protocol MI definition in ABSORB III. Table 6.1-9 shows peri-procedural MIs stratified by the magnitude of CK-MB elevation. The observed rates of peri-procedural MI were generally similar between the BVS group and the XIENCE group for each strata of CK-MB elevation.

Table 6.1-9. Peri-procedural MI Based on Different Cardiac Biomarker Elevations – Per-Subject Analysis (Primary Analysis Group, ITT Population)

CK-MB Elevation	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
>3x ULN	6.8% (89/1315)	6.6% (45/682)	0.17% [-2.28%, 2.38%]
>5x ULN	3.0% (40/1315)	2.8% (19/682)	0.26% [-1.47%, 1.72%]
>8x ULN	1.3% (17/1315)	1.3% (9/682)	0.03% [-1.29%, 0.96%]
>10x ULN	0.9% (12/1315)	1.2% (8/682)	-0.26% [-1.45%, 0.63%]

[1] Without multiplicity adjustment.

Scaffold/Stent Thrombosis

The rate and timing of ARC definite plus probable scaffold/stent thrombosis events in ABSORB III are shown in Table 6.1-10.

Table 6.1-10. Adjudicated Scaffold/Stent Thrombosis through 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per ARC Definition)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
Acute Scaffold/Stent Thrombosis (≤ 1 Day)			
Definite	0.15% (2/1320)	0.58% (4/686)	-0.43% [-1.34%, 0.10%]
Definite + Probable	0.15% (2/1320)	0.58% (4/686)	-0.43% [-1.34%, 0.10%]
Acute/Subacute Scaffold/Stent Thrombosis (0 to 30 Days)			
Definite	0.91% (12/1315)	0.73% (5/686)	0.18% [-0.86%, 0.98%]
Definite + Probable	1.06% (14/1315)	0.73% (5/686)	0.34% [-0.72%, 1.16%]
Cumulative Scaffold/Stent Thrombosis through 393 Days (0 to 393 Days)			
Definite	1.38% (18/1301)	0.74% (5/675)	0.64% [-0.46%, 1.54%]
Definite + Probable	1.54% (20/1301)	0.74% (5/675)	0.80% [-0.32%, 1.72%]

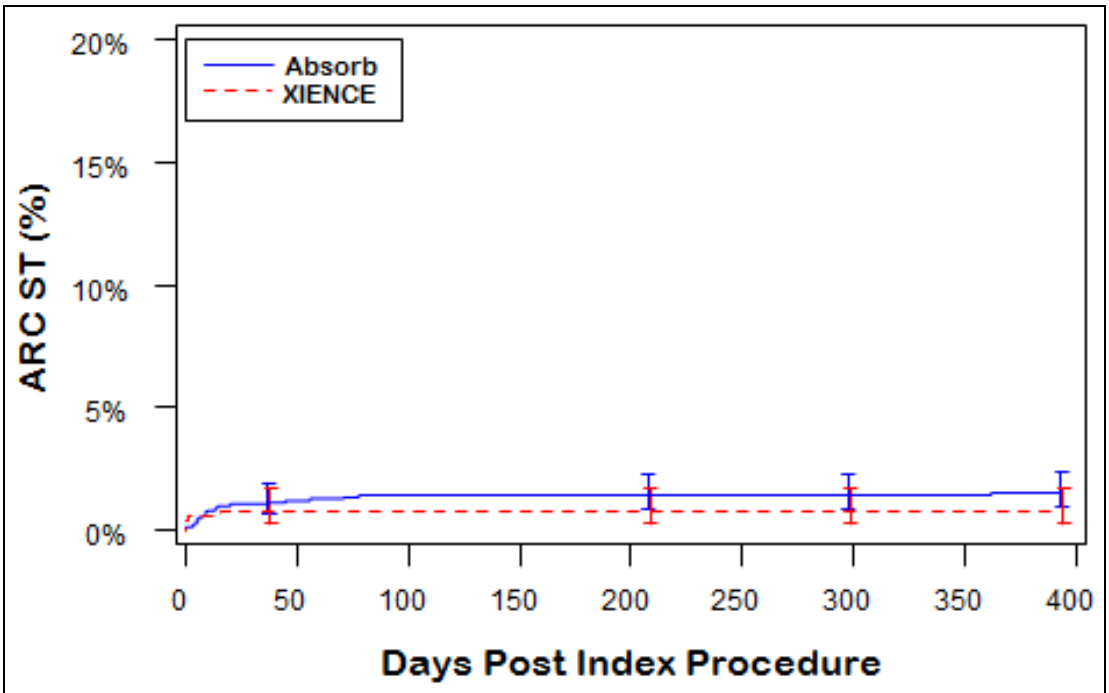
[1] Without multiplicity adjustment.

Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through a given time point without any Stent/Scaffold Thrombosis event. Note: N is the total number of subjects.

The cumulative rate of ARC definite plus probable scaffold/stent thrombosis at 1 year was >2-fold higher in the BVS group vs. the XIENCE stent group.

- BVS: 6 of the 20 definite plus probable scaffold thrombosis events occurred between 30 and 393 days following the index procedure
- XIENCE: All 5 definite plus probable stent thrombosis events occurred within 30 days of the index procedure.

A Kaplan-Meier plot of ARC definite plus probable scaffold/stent thrombosis through 1-year is shown in Figure 6.1-7.



Time After Index Procedure (days)						
		0	37	208	298	393
BVS	**# At Risk**	1322	1298	1286	1284	1271
	# Events	2	15	19	19	20
	% Survived	99.8%	98.9%	98.6%	98.6%	98.5%
	% SEM	0.1%	0.3%	0.3%	0.3%	0.3%
XIENCE	**# At Risk**	686	678	674	673	669
	# Events	3	5	5	5	5
	% Survived	99.6%	99.3%	99.3%	99.3%	99.3%
	% SEM	0.3%	0.3%	0.3%	0.3%	0.3%

Note: p = 0.1334 for the Log-Rank test comparing the survival curves for definite or probable stent/scaffold thrombosis (per ARC definition) through 1 year between the two study groups. This test was not pre-specified in the study protocol and was not adjusted for multiplicity.

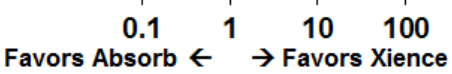
Figure 6.1-7. Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of Definite or Probable Stent/Scaffold Thrombosis (Per ARC Definition) through 1 Year (Primary Analysis Group, ITT Population)

Subgroup Analysis of Definite/Probable Scaffold/Stent Thrombosis

Table 6.1-11 shows the rate of ARC definite plus probable scaffold/stent thrombosis for the BVS vs. XIENCE groups for various subgroups. Most relative risks were numerically higher in the BVS group.

Table 6.1-11. 1 Year Define/Probable Stent/Scaffold Thrombosis: Subgroup Analysis

Subgroup	Absorb N=1322	Xience N=686	Relative Risk (95% CI)
Age ≥64	1.8	0.6	**3.22** (0.73, 14.32)
Age <64	1.2	0.9	**1.33** (0.36, 4.99)
Female	1.6	2.0	**0.79** (0.23, 2.78)
Male	1.5	0.2	**7.21** (0.95, 54.63)
Diabetes	3.2	1.4	**2.34** (0.67, 8.13)
No Diabetes	0.8	0.4	**1.79** (0.37, 8.56)
Unstable Angina/Recent MI	1.0	0.6	**1.88** (0.21, 16.74)
Stable CAD	1.7	0.8	**2.16** (0.73, 6.42)
Single Lesion Treated	1.6	0.8	**2.09** (0.79, 5.55)
Dual Lesion Treated	0.0	0.0	(nc) (nc)
Clopidogrel	1.8	0.7	**2.69** (0.78, 9.24)
Prasugrel or Ticagrelor	0.8	0.9	**0.96** (0.18, 5.2)
ACC/AHA Class A or B1	0.8	0.6	**1.36** (0.14, 12.98)
ACC/AHA Class B2 or C	1.9	0.8	**2.32** (0.79, 6.87)
Lesion Length < 11.75 mm	1.4	0.9	**1.58** (0.43, 5.78)
Lesion Length ≥ 11.75 mm	1.7	0.6	**2.82** (0.63, 12.67)
Vessel Diameter < 2.63 mm	2.3	0.9	**2.65** (0.77, 9.07)
Vessel Diameter ≥ 2.63 mm	0.8	0.6	**1.28** (0.25, 6.54)



Note: The presented 95% CIs are not adjusted for multiplicity.

Clinical Events in Subjects with Scaffold/Stent Thrombosis

Clinical events associated with and following scaffold/stent thrombosis events are shown in Table 6.1-12.

Table 6.1-12. Clinical Events for Absorb and XIENCE Subjects Who Experienced a Definite or Probable ST Event (Primary Analysis Group, As Treated Population)

	BVS (n=19) (Definite ST=17, Probable ST=2)	XIENCE (n=6) (Definite ST=6, Probable ST=0)
Concurrent Events Associated with ST		
Death	11% (2/19)*	0% (0/6)
TV-MI	74% (14/19)	83% (5/6)
TV QMI	42% (8/19)	17% (1/6)
TV NQMI	32% (6/19)	67% (4/6)
Unstable Angina	21% (4/19)	100% (6/6)
ID-TLR	89% (17/19)	100% (6/6)
Subsequent Events following ST		
Cardiac Death	0% (0/17)	0% (0/6)
TV-MI	6% (1/17)	0% (0/6)
ARC def + prob ST	0% (0/17)	0% (0/6)
TVR	6% (1/17)	33% (2/6)
Rehospitalization	35% (6/17)	67% (4/6)
No event	59% (10/17)	33% (2/6)

* The 2 cases of probable ST were sudden deaths within 30 days following the index procedure.
Def + prob ST = definite plus probable scaffold/stent thrombosis

Two BVS subjects died suddenly within 30 days of the index procedure; per the ARC stent thrombosis definitions, these cases were adjudicated as probable scaffold thrombosis events. Most ARC definite plus probable scaffold/stent thrombosis events were target vessel MIs, and most of these subjects underwent target lesion revascularization. Subsequent clinical events in

scaffold/stent thrombosis subjects were uncommon in both treatment groups

Effectiveness: Ischemia-Driven Target Lesion and Target Vessel Revascularization

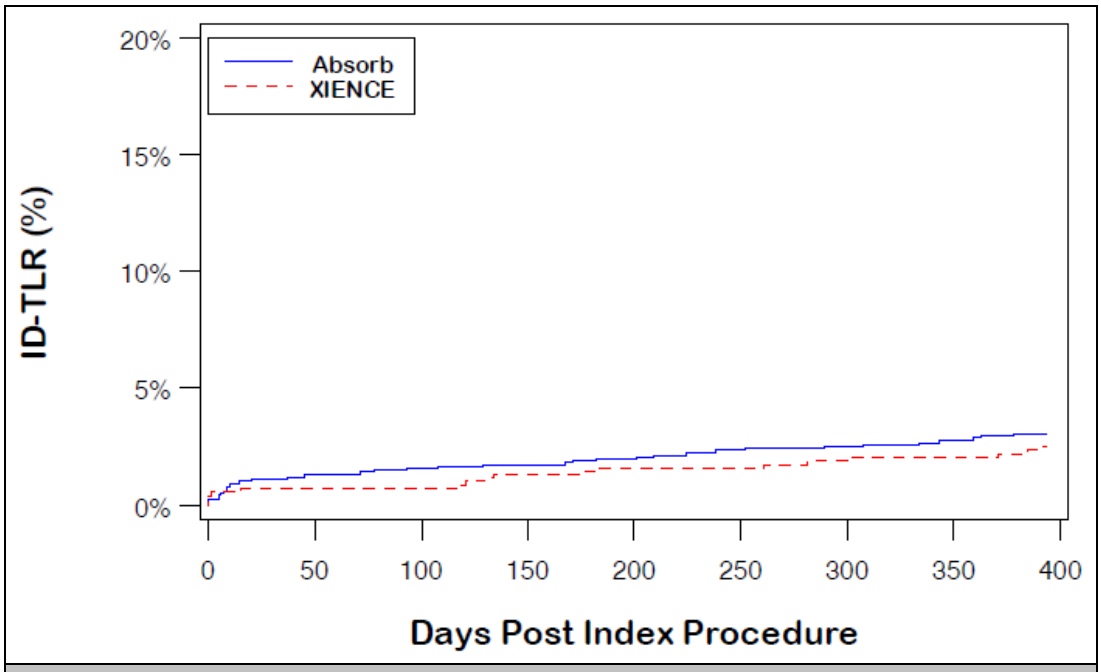
Table 6.1-13 shows the rates of ischemia-driven target lesion and target vessel revascularization at 1 year, which were generally similar between treatment groups.

Table 6.1-13. Non-Hierarchical Revascularization Events through In-Hospital, at 30 days, at 180 days and at 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
In-Hospital (Peri-procedural)			
ID-TLR	0.3% (4/1319)	0.6% (4/686)	-0.28% [-1.21%, 0.31%]
ID-TVR excluding TLR	0.1% (1/1319)	0.0% (0/686)	0.08% [-0.48%, 0.43%]
0 to 30 Days			
ID-TLR	1.2% (16/1317)	0.7% (5/686)	0.49% [-0.59%, 1.34%]
ID-TVR excluding TLR	0.2% (3/1317)	0.0% (0/686)	0.23% [-0.35%, 0.67%]
0 to 180 days			
ID-TLR	2.1% (27/1315)	1.6% (11/681)	0.44% [-0.97%, 1.60%]
ID-TVR excluding TLR	1.3% (17/1315)	0.3% (2/681)	1.00% [0.09%, 1.80%]
Cumulative to 1-Year			
ID-TLR	3.0% (40/1313)	2.5% (17/677)	0.54% [-1.14%, 1.96%]
ID-TVR excluding TLR	2.4% (32/1313)	1.8% (12/677)	0.66% [-0.81%, 1.90%]

[1] Without multiplicity adjustment.

A Kaplan Meier curve of ischemia-driven target lesion revascularization is shown in Figure 6.1-8.



Time After Index Procedure (days)						
		0	**37**	**208**	**298**	**393**
BVS	**# At Risk**	1322	1295	1276	1268	1249
	# Events	3	16	27	33	40
	% Survived	99.8%	98.8%	97.9%	97.5%	96.9%
	% SEM	0.1%	0.3%	0.4%	0.4%	0.5%
XIENCE	**# At Risk**	686	678	668	665	657
	# Events	3	5	11	13	17
	% Survived	99.6%	99.3%	98.4%	98.1%	97.5%
	% SEM	0.3%	0.3%	0.5%	0.5%	0.6%

Note: p = 0.4720 for the Log-Rank test comparing the survival curves for ID-TLR through 1 year between the two study groups. This test was not pre-specified in the study protocol and was not adjusted for multiplicity.

Figure 6.1-8. Kaplan-Meier Curves Representing the Estimated Cumulative Incidence Rates of ID-TLR through 1 Year (Primary Analysis Group, ITT Population)

6.1.2.3 Secondary Endpoints with Pre-Specified Hypothesis Tests: Other Effectiveness Endpoints

The results of the pre-specified hypothesis tests of angina, all revascularization and ID-TVR at 1 year for the ITT population are shown in the Table 6.1-14a. Of note, for the angina endpoint, angina was defined as the first adverse event resulting in the *site diagnosis of angina* (excluding angina occurring within the first 7 days following the index procedure). According to the pre-specified testing sequence, further testing stopped after the superiority hypothesis test of 1-year angina was not passed in the ITT population. Superiority was not met for any of the secondary endpoints with pre-specified hypothesis tests in the ITT population.

Table 6.1-14a. Analysis of Secondary Endpoints with Pre-Specified Hypothesis Tests – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	BVS (N=1322)	XIENCE (N=686)	Difference [95% CL][4]	Superiority P-Value
1-Year Angina[1]	18.3% (238/1303)	18.4% (125/678)	-0.17% [-3.77%, 3.42%]	0.9256
1-Year All Revascularization[2]	9.1% (120/1313)	8.1% (55/677)	1.02% [-1.57%, 3.60%]	NA[5]
1-Year ID-TVR[3]	5.0% (66/1313)	3.7% (25/677)	1.33% [-0.51%, 3.18%]	NA[5]

[1] First reported angina post discharge. Excluding angina following the index procedure through discharge, not to exceed a period of 7 days.
[2] Includes TLR, TVR excluding TLR, and non TVR.
[3] Ischemia driven target vessel revascularization.
[4] Without multiplicity adjustment.
[5] According to the pre-specified testing sequence, further testing stopped after the superiority hypothesis test of 1-year angina was not passed. The superiority hypothesis tests of 1-year all revascularization and 1-year ID-TVR were not passed.
Note: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without DMR (death, MI, or revascularization.
Note: 1-year timeframe includes a window of ± 28 days.

The results of the pre-specified hypothesis tests of angina, all revascularization and ID-TVR at 1 year for the PTE population are shown in the Table 6.1-14b. According to the pre-specified testing sequence, further testing stopped after the superiority hypothesis test of 1-year angina was not passed in the PTE population. Superiority was not met for any of the secondary endpoints with pre-specified hypothesis tests in the PTE population.

Table 6.1-14b. Analysis of Secondary Endpoints with Pre-Specified Hypothesis Tests – Per-Subject Analysis (Primary Analysis Group, PTE Population)

	BVS (N=1180)	XIENCE (N=679)	Difference [95% CL][4]	Superiority P-Value
1-Year Angina[1]	17.4% (203/1164)	19.0% (127/670)	-1.52% [-5.20%, 2.17%]	0.4159
1-Year All Revascularization[2]	8.2% (96/1174)	8.4% (56/670)	-0.18% [-2.80%, 2.44%]	NA[5]
1-Year ID-TVR[3]	4.9% (57/1174)	3.7% (25/670)	1.12% [-0.77%, 3.01%]	NA[5]

[1] First reported angina post discharge. Excluding angina following the index procedure through discharge, not to exceed a period of 7 days.
[2] Includes TLR, TVR excluding TLR, and non TVR.
[3] Ischemia driven target vessel revascularization.
[4] Without multiplicity adjustment.
[5] According to the pre-specified testing sequence, further testing stopped after the superiority hypothesis test of 1-year angina was not passed. The superiority hypothesis tests of 1-year all revascularization and 1-year ID-TVR were not passed.
Note: For the angina endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without any angina event. For the all revascularization endpoint, denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without DMR (death, MI, or revascularization).
Note: 1-year timeframe includes a window of ± 28 days.

6.1.2.4 Scaffold/Stent Implantation Endpoints: Clinical Device and Clinical Procedure Success

Clinical device success

- Assessed on a per-lesion basis
- Defined as the successful delivery and deployment of the study scaffold/stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/stent residual stenosis of <30% by QCA (or by visual estimation if QCA unavailable).
    - The need for bailout procedures with additional scaffolds of stents was not considered in the determination of clinical device success or failure.

Clinical procedure success

- Assessed on a per-subject basis
- Defined as the achievement of final in-scaffold/stent residual stenosis of <30% by QCA (or by visual estimation if QCA unavailable) with successful delivery and deployment of at least one study scaffold/stent at the intended target lesion and successful withdrawal of the delivery system for all target lesions without the occurrence of cardiac death, target vessel MI or repeat TLR during the hospital stay (to a maximum of 7 days).
- In dual target lesion treatment, both lesions must meet clinical procedure success criteria to be considered a clinical procedure success

The clinical device and clinical procedure success rates are shown in Table 6.1-15.

Table 6.1-15. Acute Success (Primary Analysis Group, ITT Population)

	BVS (N=1322), (L=1385)	XIENCE (N=686), (L=713)	Difference [95% CI][1]
Clinical Device Success [95% Confidence Interval][1]	94.3% (1278/1355) [92.95%, 95.49%]	99.3% (699/704) [98.35%, 99.77%]	-4.97% [-6.39%, -3.52%]
Clinical Procedure Success [95% Confidence Interval][1]	94.6% (1240/1311) [93.22%, 95.75%]	96.2% (652/678) [94.43%, 97.48%]	-1.58% [-3.40%, 0.46%]

[1] Without multiplicity adjustment. Note: N=number of subjects. L=Number of lesions.
Note: Clinical device success is computed per lesion and clinical procedure success is computed per subject.

The numerically lower clinical device success rate seen in the BVS group was driven by the inability of the study device to be delivered to the lesion site and cases in which the residual post-procedure in-device diameter stenosis was ≥30%.

6.1.2.5 Patient-Reported Outcomes Endpoint

Patient-reported outcomes (PRO) was an informational endpoint to assess health-related quality of life at baseline, 30 days, 1, 2, 3, 4 and 5 years follow-up. The following questionnaires were used:

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

These patient-reported outcomes at 1 year appeared similar between the BVS and XIENCE groups.

6.1.2.6 Analysis of Pre-Specified Subgroups

The evaluation of the 12 month TLF rate within subgroups that were pre-specified in the Statistical Analysis Plan is shown in Table 6.1-16. The TLF rates numerically favored the XIENCE group for most analyses.

Table 6.1-16. Subgroup Analysis of TLF through 1 Year – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	BVS (N=1322)	XIENCE (N=686)	Relative Risk [95% CI][5]	Difference [95% CI][5]
Overall ITT Population	7.8% (102/1313)	6.1% (41/677)	1.28 [0.90, 1.82]	1.71% [-0.74%, 3.93%]
Female	8.5% (33/386)	7.4% (15/203)	1.16 [0.64, 2.08]	1.16% [-3.89%, 5.46%]
Male	7.4% (69/927)	5.5% (26/474)	1.36 [0.88, 2.10]	1.96% [-0.91%, 4.50%]
All Diabetes Mellitus	10.7% (44/411)	9.1% (20/220)	1.18 [0.71, 1.95]	1.61% [-3.63%, 6.21%]
No Diabetes Mellitus	6.3% (57/900)	4.6% (21/457)	1.38 [0.85, 2.24]	1.74% [-0.98%, 4.11%]
MTDM[1]	11.1% (41/368)	9.3% (18/193)	1.19 [0.71, 2.02]	1.81% [-3.87%, 6.75%]
NMTDM[2]	7.0% (3/43)	7.4% (2/27)	0.94 [0.17, 5.28]	-0.43% [-17.04%, 12.37%]
ITDM[3]	15.6% (21/135)	13.2% (10/76)	1.18 [0.59, 2.38]	2.40% [-8.32%, 11.56%]
NITDM[4]	8.3% (23/276)	6.9% (10/144)	1.20 [0.59, 2.45]	1.39% [-4.63%, 6.36%]
Non-White	8.3% (14/169)	6.4% (5/78)	1.29 [0.48, 3.46]	1.87% [-6.53%, 8.17%]
White	7.7% (88/1144)	6.0% (36/599)	1.28 [0.88, 1.86]	1.68% [-0.93%, 4.04%]
Age ≥ Median	8.1% (54/665)	5.9% (21/355)	1.37 [0.84, 2.23]	2.20% [-1.28%, 5.28%]
Age < Median	7.4% (48/648)	6.2% (20/322)	1.19 [0.72, 1.97]	1.20% [-2.45%, 4.33%]
Age ≥ 65	8.6% (54/631)	5.5% (18/330)	1.57 [0.94, 2.63]	3.10% [-0.47%, 6.24%]
Age < 65	7.0% (48/682)	6.6% (23/347)	1.06 [0.66, 1.72]	0.41% [-3.14%, 3.48%]
Single Target Lesion/ Vessel Treated	7.4% (82/1104)	5.2% (29/562)	1.44 [0.95, 2.17]	2.27% [-0.30%, 4.56%]

	BVS	XIENCE	Relative Risk	Difference
Dual Target Lesion/ Vessel Treated	8.6% (5/58)	12.0% (3/25)	0.72 [0.19, 2.78]	-3.38% [-21.99%, 9.34%]
One Target Lesion/Vessel & One Non-target Lesion/Vessel Treated	8.7% (11/126)	10.7% (8/75)	0.82 [0.34, 1.94]	-1.94% [-11.70%, 6.15%]
Stable Angina or Silent Ischemia	8.5% (75/886)	6.0% (29/484)	1.41 [0.93, 2.14]	2.47% [-0.51%, 5.17%]
Unstable Angina	5.7% (20/350)	6.7% (11/163)	0.85 [0.42, 1.73]	-1.03% [-6.35%, 3.13%]
Stable Angina	8.9% (67/755)	6.3% (26/415)	1.42 [0.92, 2.19]	2.61% [-0.70%, 5.58%]
Silent Ischemia	6.1% (8/131)	4.3% (3/69)	1.40 [0.38, 5.13]	1.76% [-6.47%, 7.94%]

[1] MTDM=Medication Treated Diabetes Mellitus.
[2] NMTDM=Non-Medically Treated Diabetes Mellitus.
[3] ITDM=Insulin-Treated Diabetes Mellitus.
[4] NITDM=Non-Insulin Treated Diabetes Mellitus.
[5] Without multiplicity adjustment.
Note: Subjects are only counted once for each type of event in each time period.
Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through 1 year without DMR (death, MI, or revascularization).
Note: The median age of primary analysis group is 64.

6.1.2.7 Gender Analysis

Table 6.1-17 shows the rates of TLF (and its components) and ARC definite plus probable scaffold/stent thrombosis stratified by gender. The event rates in BVS-treated subjects were generally similar in men and women.

Table 6.1-17. ABSORB III Primary Analysis Group: TLF, TLF Components and ST by Gender – 1-Year Outcomes

	Female			Male		
	BVS (N=388)	XIENCE (N=205)	Difference [95% CI][1]	BVS (N=934)	XIENCE (N=481)	Difference [95% CI][1]
Target Lesion Failure	8.5% (33/386)	7.4% (15/203)	1.16% [-3.89%, 5.46%]	7.4% (69/927)	5.5% (26/474)	1.96% [-0.91%, 4.50%]
Cardiac Death	0.3% (1/386)	0.0% (0/203)	0.26% [-1.61%, 1.45%]	0.8% (7/927)	0.2% (1/474)	0.54% [-0.50%, 1.36%]
Target Vessel MI	7.3% (28/386)	5.4% (11/203)	1.84% [-2.74%, 5.68%]	5.5% (51/927)	4.2% (20/474)	1.28% [-1.28%, 3.50%]
ID-TLR	3.4% (13/386)	3.9% (8/203)	-0.57% [-4.47%, 2.44%]	2.9% (27/927)	1.9% (9/474)	1.01% [-0.88%, 2.59%]
Def+Prob Scaffold/ Stent Thrombosis	1.56% (6/384)	1.97% (4/203)	-0.41% [-3.51%, 1.76%]	1.53% (14/917)	0.21% (1/472)	1.31% [0.16%, 2.35%]

[1]Without multiplicity adjustment.
Note: Def+Prob = ARC definite + probable stent thrombosis; ID-TLR = ischemia-driven target revascularization.

FDA Comment: The Advisory Panel will be asked to consider whether the ABSORB III data provide adequate evidence of the clinical non-inferiority of the BVS compared to the XIENCE stent with regard to (A) safety and (B) effectiveness in the patient population described by the proposed indications for use.

6.1.2.8 Small Vessel Subgroup Post-Hoc Analysis

In the ABSORB III trial, a target vessel size inclusion criterion was a reference vessel diameter (RVD) determined following pre-dilatation of ≥2.5 mm (as visually assessed by the operator). It is recognized that visual estimates of coronary artery dimensions typically overestimate true vessel diameters as measured by angiographic core labs using quantitative coronary angiography (QCA). Although the precise overestimation of vessel diameters by visual assessment is not known, 0.25 mm is a reasonable approximation, such that a 2.50 mm visually estimated diameter correlates with a 2.25 mm QCA-measured diameter.

In ABSORB III, the angiographic core laboratory found that 19% (375/1998) of ITT subjects (18% (242/1316) and 20% (133/682) of BVS and XIENCE subjects, respectively) underwent treatment of an artery <2.25 mm in QCA-assessed diameter.

Baseline clinical, angiographic, and procedural characteristics for the ≥2.25 mm and <2.25 mm RVD subgroups were similar between the BVS and XIENCE groups (Table 6.1-18 a, b and c). , There were few differences in baseline variables between the BVS and XIENCE group stratified by a QCA-assessed RVD of <2.25 mm or ≥2.25 mm. The post-scaffold/stent implantation percent diameter stenosis was numerically greater in the BVS group vs. the XIENCE group for RVDs <2.25 mm and ≥2.25 mm. The in-device minimal lumen diameter, in-device acute gain, and total stented/scaffold length were numerically smaller in the BVS group vs. the XIENCE group for RVDs <2.25 mm and ≥2.25 mm.

Table 6.1-18a. Baseline Patient Characteristics and Risk Factors Stratified by Core Laboratory-Assessed RVD – Per-Subject Analysis (Primary Analysis Group, ITT Population)

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074)	XIENCE (N=549)	Difference [95% CI][1]	BVS (N=242)	XIENCE (N=133)	Difference [95% CI][1]
Age (year)	63.3 ± 10.6 (1074)	63.3 ± 10.2 (549)	-0.0 [-1.1, 1.0]	64.5 ± 10.9 (242)	64.9 ± 10.7 (133)	-0.4 [-2.7, 1.9]
Male Subjects	71.5% (768/1074)	73.0% (401/549)	-1.53% [-6.03%, 3.13%]	66.5% (161/242)	57.1% (76/133)	9.39% [-0.79%, 19.59%]
Body Mass Index (kg/m^2)	30.78 ± 6.25 (1074)	30.54 ± 6.22 (549)	0.24 [-0.40, 0.88]	29.67 ± 5.90 (242)	30.11 ± 6.48 (133)	-0.44 [-1.77, 0.90]
Current Tobacco Use	20.9% (224/1074)	20.2% (111/549)	0.64% [-3.61%, 4.68%]	22.3% (54/242)	22.6% (30/133)	-0.24% [-9.41%, 8.20%]
Any Diabetes Mellitus (DM)	30.3% (325/1073)	32.2% (177/549)	-1.95% [-6.78%, 2.76%]	36.5% (88/241)	33.8% (45/133)	2.68% [-7.54%, 12.43%]
DM req. Med.	21.8% (234/1073)	22.8% (125/549)	-0.96% [-5.34%, 3.23%]	29.0% (70/241)	26.3% (35/133)	2.73% [-6.96%, 11.77%]
DM req. Insulin	10.1% (108/1073)	11.7% (64/549)	-1.59% [-4.98%, 1.51%]	11.2% (27/241)	9.8% (13/133)	1.43% [-5.66%, 7.51%]
HbA1c (%) (All Diabetes Mellitus)	7.52 ± 1.76 (303)	7.78 ± 2.01 (163)	-0.26 [-0.62, 0.11]	7.66 ± 1.81 (84)	7.87 ± 2.26 (44)	-0.20 [-0.99, 0.58]

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074)	**XIENCE (N=549)**	**Difference [95% CI][1]**	**BVS (N=242)**	**XIENCE (N=133)**	**Difference [95% CI][1]**
Hypertension req. Med.	80.5% (865/1074)	80.0% (439/549)	0.58% [-3.42%, 4.78%]	83.5% (202/242)	84.2% (112/133)	-0.74% [-8.11%, 7.52%]
Dyslipidemia req. Med.	75.9% (815/1074)	77.8% (427/549)	-1.89% [-6.11%, 2.52%]	78.1% (189/242)	77.4% (103/133)	0.66% [-7.77%, 9.80%]
Prior Coronary Intervention	37.4% (402/1074)	37.5% (206/549)	-0.09% [-5.10%, 4.83%]	45.0% (109/242)	41.2% (54/131)	3.82% [-6.72%, 14.05%]
Prior MI	21.1% (225/1066)	20.5% (112/546)	0.59% [-3.69%, 4.67%]	23.4% (56/239)	29.0% (38/131)	-5.58% [-15.21%, 3.56%]
Cardiac Status						
AMI	3.1% (33/1073)	2.0% (11/549)	1.07% [-0.71%, 2.57%]	1.7% (4/242)	5.3% (7/133)	-3.61% [-8.91%, 0.08%]
Unstable Angina	27.1% (291/1073)	26.2% (144/549)	0.89% [-3.73%, 5.34%]	25.6% (62/242)	18.0% (24/133)	7.57% [-1.41%, 15.68%]
Stable Angina	57.2% (614/1073)	59.9% (329/549)	-2.70% [-7.71%, 2.38%]	57.4% (139/242)	63.9% (85/133)	-6.47% [-16.39%, 3.93%]
Silent Ischemia	9.8% (105/1073)	10.2% (56/549)	-0.41% [-3.67%, 2.55%]	11.2% (27/242)	9.8% (13/133)	1.38% [-5.70%, 7.45%]
No Current Evidence of Ischemia	2.2% (24/1073)	0.9% (5/549)	1.33% [-0.08%, 2.52%]	1.7% (4/242)	3.0% (4/133)	-1.35% [-5.94%, 1.76%]
Single diseased artery	71.0% (763/1074)	70.5% (387/549)	0.55% [-4.05%, 5.30%]	63.6% (154/242)	54.9% (73/133)	8.75% [-1.55%, 19.02%]
Two diseased arteries	22.9% (246/1074)	23.7% (130/549)	-0.77% [-5.22%, 3.48%]	29.8% (72/242)	36.8% (49/133)	-7.09% [-17.13%, 2.71%]
Three or more diseased arteries	6.1% (65/1074)	5.8% (32/549)	0.22% [-2.39%, 2.53%]	6.6% (16/242)	8.3% (11/133)	-1.66% [-8.10%, 3.61%]

[1] Without multiplicity adjustment.
Note: N=number of subjects

Table 6.1-18b. Baseline Lesion Characteristics and QCA by Angiographic Core Lab Stratified by Core Laboratory-Assessed RVD – Per-Subject / Per-Lesion Analysis (ITT Population)

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074) (L=1115)	**XIENCE (N=549) (L=561)**	**Difference [95% CI][1]**	**BVS (N=242) (L=262)**	**XIENCE (N=133) (L=146)**	**Difference [95% CI][1]**
Target vessels						
Number of Target Lesions Treated	1.0 ± 0.2 (1074)	1.0 ± 0.1 (549)	0.0 [-0.0, 0.0]	1.1 ± 0.3 (242)	1.1 ± 0.3 (133)	-0.0 [-0.1, 0.0]
LAD	42.8% (477/1115)	40.3% (226/561)	2.50% [-2.52%, 7.43%]	52.3% (137/262)	50.0% (73/146)	2.29% [-7.74%, 12.28%]
LCX/Ramus	24.4% (272/1115)	29.6% (166/561)	-5.20% [-9.80%, -0.73%]	33.6% (88/262)	34.2% (50/146)	-0.66% [-10.35%, 8.67%]
RCA	32.7% (365/1115)	30.1% (169/561)	2.61% [-2.15%, 7.22%]	14.1% (37/262)	15.8% (23/146)	-1.63% [-9.35%, 5.27%]
LMCA	0.1% (1/1115)	0.0% (0/561)	0.09% [-0.59%, 0.51%]	0.0% (0/262)	0.0% (0/146)	0.00% [-2.56%, 1.45%]
Lesion Morphology						
Type B2/C	70.9% (791/1115)	76.1% (427/561)	-5.17% [-9.49%, -0.66%]	58.8% (154/262)	57.9% (84/145)	0.85% [-8.96%, 10.84%]

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074) (L=1115)	**XIENCE (N=549) (L=561)**	**Difference [95% CI][1]**	**BVS (N=242) (L=262)**	**XIENCE (N=133) (L=146)**	**Difference [95% CI][1]**
Calcification (moderate/severe)	34.6% (385/1114)	33.5% (188/561)	1.05% [-3.80%, 5.78%]	27.1% (71/262)	26.9% (39/145)	0.20% [-9.03%, 8.88%]
Bifurcations	40.5% (452/1115)	42.0% (235/560)	-1.43% [-6.44%, 3.54%]	21.8% (57/262)	19.4% (28/144)	2.31% [-6.23%, 10.11%]
Tortuosity (moderate/severe)	3.1% (35/1115)	3.7% (21/561)	-0.60% [-2.71%, 1.15%]	1.9% (5/262)	4.8% (7/145)	-2.92% [-7.84%, 0.58%]
Eccentric Lesion	76.3% (851/1115)	77.0% (432/561)	-0.68% [-4.87%, 3.69%]	73.7% (193/262)	71.0% (103/145)	2.63% [-6.18%, 11.92%]
Pre-Procedure Measurement by QCA						
Lesion Length (mm)	12.84 ± 5.36 (1113)	13.30 ± 5.57 (561)	-0.46 [-1.02, 0.10]	11.54 ± 5.46 (262)	12.45 ± 6.72 (145)	-0.91 [-2.20, 0.37]
RVD (mm)	2.80 ± 0.38 (1115)	2.79 ± 0.39 (561)	0.01 [-0.03, 0.05]	2.09 ± 0.26 (262)	2.08 ± 0.22 (145)	0.01 [-0.04, 0.06]
MLD (mm)	0.97 ± 0.38 (1115)	0.95 ± 0.35 (561)	0.02 [-0.02, 0.06]	0.72 ± 0.26 (262)	0.70 ± 0.22 (145)	0.02 [-0.03, 0.07]
%DS	65.22 ± 12.61 (1115)	65.78 ± 11.86 (561)	-0.57 [-1.80, 0.66]	65.48 ± 11.94 (262)	66.21 ± 10.87 (145)	-0.72 [-3.02, 1.57]

[1] Without multiplicity adjustment.
N=number of subjects. L=Number of lesions.

Table 6.1-18c. Procedural QCA Results by Angiographic Core Lab Stratified by Core Laboratory-Assessed RVD – Per-Lesion Analysis (Primary Analysis Group, ITT Population)

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074) (L=1115)	**XIENCE (N=549) (L=561)**	**Difference [95% CI][1]**	**BVS (N=242) (L=262)**	**XIENCE (N=133) (L=146)**	**Difference [95% CI][1]**
Post-Pre-Dilatation Measurement by QCA*						
RVD (mm)	2.80 ± 0.39 (1052)	2.80 ± 0.40 (514)	0.00 [-0.04, 0.04]	2.11 ± 0.26 (247)	2.12 ± 0.22 (133)	-0.01 [-0.06, 0.04]
MLD (mm)	1.63 ± 0.44 (1052)	1.59 ± 0.43 (514)	0.04 [-0.00, 0.09]	1.24 ± 0.34 (247)	1.22 ± 0.30 (133)	0.02 [-0.05, 0.08]
%DS	41.57 ± 14.37 (1052)	43.09 ± 13.95 (514)	-1.52 [-3.01, -0.03]	40.73 ± 15.20 (247)	41.84 ± 14.34 (133)	-1.11 [-4.21, 1.99]
Post-Scaffold/Stent Implantation Measurement by QCA						
RVD (mm)	2.82 ± 0.39 (1110)	2.82 ± 0.41 (560)	0.01 [-0.03, 0.05]	2.15 ± 0.27 (260)	2.13 ± 0.23 (144)	0.02 [-0.03, 0.07]
In-Segment MLD (mm)	2.26 ± 0.37 (1110)	2.25 ± 0.39 (560)	0.00 [-0.04, 0.04]	1.72 ± 0.27 (260)	1.71 ± 0.25 (144)	0.00 [-0.05, 0.06]
In-Segment %DS	20.03 ± 7.95 (1110)	19.90 ± 8.11 (560)	0.12 [-0.70, 0.94]	20.10 ± 7.95 (260)	19.49 ± 8.51 (144)	0.61 [-1.09, 2.31]
In-Segment Acute Gain (mm)	1.28 ± 0.46 (1110)	1.30 ± 0.46 (560)	-0.02 [-0.06, 0.03]	1.00 ± 0.36 (260)	1.01 ± 0.31 (144)	-0.02 [-0.08, 0.05]
In-Device MLD (mm)	2.47 ± 0.36 (1109)	2.60 ± 0.36 (560)	-0.13 [-0.16, -0.09]	1.95 ± 0.28 (260)	2.06 ± 0.23 (144)	-0.12 [-0.17, -0.06]
In-Device %DS	12.19 ± 8.48 (1105)	7.33 ± 8.55 (556)	4.87 [4.00, 5.74]	9.21 ± 9.55 (260)	2.82 ± 9.44 (144)	6.39 [4.46, 8.33]

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074) (L=1115)	XIENCE (N=549) (L=561)	Difference [95% CI][1]	BVS (N=242) (L=262)	XIENCE (N=133) (L=146)	Difference [95% CI][1]
In-Device Acute Gain (mm)	1.50 ± 0.45 (1109)	1.65 ± 0.44 (560)	-0.15 [-0.19, -0.10]	1.23 ± 0.37 (260)	1.36 ± 0.32 (144)	-0.13 [-0.20, -0.06]
Total Stented/ Scaffold Length (mm)	18.20 ± 6.41 (1109)	19.13 ± 7.37 (560)	-0.94 [-1.65, -0.22]	17.25 ± 6.47 (260)	19.22 ± 8.56 (144)	-1.97 [-3.59, -0.36]

[1] Without multiplicity adjustment.
*Post-Pre-Dilatation Measurement by QCA refers to measurements performed after completion of lesion pre-dilatation.
N=number of subjects. L=Number of lesions.

Table 6.1-19 shows the rates of 1-year TLF, the components of TLF, and ARC definite plus probable stent thrombosis for the BVS vs. XIENCE groups, stratified by a QCA-assessed RVD ≥2.25 mm or <2.25 mm.

Table 6.1-19. 1 Year Clinical Outcomes Stratified by Core Laboratory-Assessed RVD – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	RVD ≥2.25 mm			RVD <2.25 mm		
	BVS (N=1074)	XIENCE (N=549)	Difference [95% CI][1]	BVS (N=242)	XIENCE (N=133)	Difference [95% CI][1]
Pre-procedure median RVD by QCA (mm)	2.75	2.72	N/A	2.08	2.10	N/A
Target Lesion Failure	6.7% (71/1067)	5.5% (30/542)	1.12% [-1.51%, 3.44%]	12.9% (31/241)	8.3% (11/133)	4.59% [-2.37%, 10.60%]
Cardiac Death	0.6% (6/1067)	0.2% (1/542)	0.38% [-0.53%, 1.05%]	0.8% (2/241)	0.0% (0/133)	0.83% [-2.04%, 2.97%]
Target Vessel MI	5.2% (55/1067)	4.6% (25/542)	0.54% [-1.87%, 2.64%]	10.0% (24/241)	4.5% (6/133)	5.45% [-0.46%, 10.50%]
ID-TLR	2.2% (24/1067)	1.5% (8/542)	0.77% [-0.82%, 2.07%]	6.6% (16/241)	6.8% (9/133)	-0.13% [-6.26%, 4.87%]
Def+Prob Scaffold/Stent Thrombosis	0.85% (9/1058)	0.56% (3/540)	0.30% [-0.84%, 1.14%]	4.62% (11/238)	1.50% (2/133)	3.12% [-1.20%, 6.75%]

[1] Without multiplicity adjustment.
Note: Def+Prob = ARC definite + probable stent thrombosis; ID-TLR = ischemia-driven target revascularization; QCA = quantitative coronary angiography

The event rates were higher in both treatment groups in subjects with a QCA-assessed <2.25 mm RVD diameter compared with a ≥2.25 mm RVD. However, except for ID-TLR, the differences in rates between treatment groups were greater in subjects with a <2.25 mm RVD diameter treated with a BVS vs. those treated with a XIENCE stent (most notably for TLF, target vessel MI, and scaffold/stent thrombosis).

Advanced intravascular imaging techniques to more accurately assess RVD, stent/scaffold size selection and optimal device deployment were infrequently used in ABSORB III. A quantitative assessment (IVUS, OCT, on-line QCA, or angiogram caliper) was used in 11.8% (156/1322) of BVS and 11.4% (78/686) of XIENCE subjects.

Amongst cases in which a quantitative imaging assessment was used, 15.4% (24/156) of BVS subjects had a QCA-assessed RVD of <2.25 mm. Conversely, in BVS subjects that did not have a quantitative imaging assessment, 18.4% (211/1146) had at least one lesion with a QCA-assessed RVD of <2.25 mm.

In the XIENCE group, in cases in which a quantitative imaging assessment was used, 14.1% (11/78) of subjects had a QCA-assessed RVD of <2.25 mm. In contrast, in XIENCE subjects that did not have a quantitative imaging assessment 20.2% (120/595) had at least one lesion with a QCA-assessed RVD of <2.25 mm.

The pre-procedure use of on-line QCA or IVUS were required in the ABSORB EXTEND and ABSORB II studies (and was optional in ABSORB Cohort B and ABSORB JAPAN), with the use of the imaging techniques focused primarily on selecting the correct size scaffold or stent for the vessel RVD. Nevertheless, the percentage of subjects enrolled with a QCA-assessed RVD <2.25 mm (Table 6.1-20) was generally similar to the rate of subjects with undersized target vessels enrolled in ABSORB III (19%).

Table 6.1-20. Proportion of Subjects with Small Vessel RVDs Enrolled in non-US ABSORB Studies

Pre-Procedure RVD <2.25 mm	ABSORB Cohort B (N=101),(L=102)	ABSORB EXTEND (N=812),(L=874)	ABSORB II (N=501), (L=546)	ABSORB JAPAN (N=400), (L=412)
Per Subject[1]	17.5% (17/97)	15.5% (124/799)	20.4% (102/499)	14.5% (58/400)
Per Lesion Mean ± SD (*l*) Minimum	 2.12 ± 0.09 (17) 1.98	 2.15 ± 0.25 (145) 1.37	 2.14 ± 0.23 (118) 1.41	 2.12 ± 0.12 (62) 1.66

[1] The subjects with at least one target lesion pre-procedure RVD < 2.25 mm and with all target lesion RVD ≥ 2.25 mm are included per subject analysis.

Note: RVD < 2.25 mm includes the subjects with at least one target lesion pre-procedure RVD < 2.25 mm (core-lab measurement).

Note: N is the total number of subjects; L is the total number of target lesions.

Analyses of clinical outcomes stratified by vessel a QCA-assessed RVD <2.25 mm vs. ≥2.25 mm in ABSORB Cohort B, ABSORB EXTEND, ABSORB II and ABSORB JAPAN are provided in Appendix 7. In general, higher event rates were associated with BVS implantation in undersized arteries.

FDA Comment: The Advisory Panel will be asked:

- to consider the clinical significance of the higher event rates when a BVS was implanted in an artery with a QCA-assessed RVD <2.25 mm.
- to comment on whether the following proposed precaution and warning statements that are intended to address concerns related to deployment of the Absorb GT1 BVS in vessels <2.5 mm are adequate and acceptable.
    - *<u>Precaution</u>: In small vessels (visually assessed as ≤2.75 mm), on-line QCA or intravascular imaging is strongly recommended to accurately measure and confirm appropriate vessel sizing (≥2.5 mm).*
    - *<u>Warning</u>: If quantitative imaging determines a vessel size <2.5 mm, do not implant Absorb. Implantation of the device in vessels <2.5 mm may lead to an increased risk of adverse events*

6.1.2.9 Clinical Outcomes in Subjects With Diabetes Mellitus

Subjects with diabetes mellitus are at increased cardiovascular risk compared to non-diabetics. Table 6.1-21 shows clinical outcomes in ABSORB III subjects with diabetes mellitus. As expected, event rates were higher in diabetics vs. non-diabetics in both treatment groups with numerically higher rates in the BVS group vs. XIENCE.

Table 6.1-21. 1 Year Clinical Outcomes in Subjects With and Without Diabetes Mellitus – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	Subjects With DM			Subjects Without DM		
	BVS (N=416)	XIENCE (N=224)	Difference [95% CI][1]	BVS (N=904)	XIENCE (N=462)	Difference [95% CI][1]
TLF	10.7% (44/411)	9.1% (20/220)	1.61% [-3.63%, 6.21%]	6.3% (57/900)	4.6% (21/457)	1.74% [-0.98%, 4.11%]
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.49% [-1.27%, 1.76%]	0.7% (6/900)	0.2% (1/457)	0.45% [-0.62%, 1.25%]
TV- MI	9.0% (37/411)	7.3% (16/220)	1.73% [-3.12%, 5.92%]	4.6% (41/900)	3.3% (15/457)	1.27% [-1.10%, 3.30%]
ID-TLR	5.6% (23/411)	3.6% (8/220)	1.96% [-1.88%, 5.16%]	1.8% (16/900)	2.0% (9/457)	-0.19% [-2.05%, 1.24%]
Scaffold/Stent Thrombosis	3.2% (13/405)	1.4% (3/219)	1.84% [-1.06%, 4.22%]	0.8% (7/894)	0.4% (2/456)	0.34% [-0.87%, 1.23%]

[1]Without multiplicity adjustment.
DM = diabetes mellitus. Note: N is the total number of subjects

Table 6.1-22 shows clinical outcomes in ABSORB III subjects with diabetes mellitus, stratified by insulin-requiring and non-insulin requiring status. Event rates were generally higher in insulin-requiring diabetics vs. diabetic subjects not requiring insulin in both treatment groups with most rates numerically higher in the BVS group vs. XIENCE. Of note, the number of insulin-requiring diabetics was relatively small.

Table 6.1-22. 1 Year Clinical Outcomes in Subjects With Diabetes Mellitus Stratified by Insulin-Requiring and Non-Insulin Requiring Status – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	Diabetic Subjects Requiring Insulin			Diabetic Subjects Not Requiring Insulin		
	BVS (N=138)	XIENCE (N=77)	Difference [95% CI][1]	BVS (N=278)	XIENCE (N=147)	Difference [95% CI][1]
TLF	15.6% (21/135)	13.2% (10/76)	2.40% [-8.32%, 11.56%]	8.3% (23/276)	6.9% (10/144)	1.39% [-4.63%, 6.36%]
Cardiac Death	0.0% (0/135)	0.0% (0/76)	0.00% [-4.81%, 2.77%]	0.7% (2/276)	0.0% (0/144)	0.72% [-1.93%, 2.60%]
TV- MI	14.1% (19/135)	13.2% (10/76)	0.92% [-9.67%, 9.93%]	6.5% (18/276)	4.2% (6/144)	2.36% [-2.84%, 6.55%]
ID-TLR	8.9% (12/135)	1.3% (1/76)	7.57% [0.70%, 13.68%]	4.0% (11/276)	4.9% (7/144)	-0.88% [-6.01%, 3.03%]
Scaffold/Stent Thrombosis	5.19% (7/135)	1.33% (1/75)	3.85% [-2.56%, 9.10%]	2.22% (6/270)	1.39% (2/144)	0.83% [-2.90%, 3.57%]

[1] Without multiplicity adjustment.
DM = diabetes mellitus. Note: N is the total number of subjects

Table 6.1-23 shows an additional analysis of clinical outcomes in subjects with diabetes mellitus, stratified by a QCA-assessed RVD of <2.25 mm or ≥2.25 mm.

Table 6.1-23. 1 Year Clinical Outcomes in Subjects With Diabetes Mellitus Stratified by RVD – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	All DM			All DM with RVD ≥2.25 mm			All DM with RVD <2.25 mm		
	BVS (N=416)	XIENCE (N=224)	Difference [95% CI][1]	BVS (N=325)	XIENCE (N=177)	Difference [95% CI][1]	BVS (N=88)	XIENCE (N=45)	Difference [95% CI][1]
TLF	10.7% (44/411)	9.1% (20/220)	1.61% [-3.63%, 6.21%]	7.2% (23/321)	7.5% (13/174)	-0.31% [-5.73%, 4.23%]	23.9% (21/88)	15.6% (7/45)	8.31% [-6.99%, 20.90%]
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.49% [-1.27%, 1.76%]	0.3% (1/321)	0.0% (0/174)	0.31% [-1.86%, 1.74%]	1.1% (1/88)	0.0% (0/45)	1.14% [-6.78%, 6.16%]
TV- MI	9.0% (37/411)	7.3% (16/220)	1.73% [-3.12%, 5.92%]	6.2% (20/321)	6.9% (12/174)	-0.67% [-5.90%, 3.66%]	19.3% (17/88)	8.9% (4/45)	10.43% [-3.27%, 21.31%]
ID-TLR	5.6% (23/411)	3.6% (8/220)	1.96% [-1.88%, 5.16%]	3.4% (11/321)	1.1% (2/174)	2.28% [-1.03%, 5.01%]	13.6% (12/88)	13.3% (6/45)	0.30% [-13.73%, 11.52%]
Scaffold/ Stent Thrombosis	3.2% (13/405)	1.4% (3/219)	1.84% [-1.06%, 4.22%]	1.3% (4/318)	0.6% (1/173)	0.68% [-2.05%, 2.67%]	10.6% (9/85)	4.4% (2/45)	6.14% [-5.34%, 15.07%]

[1] Without multiplicity adjustment.
DM = diabetes mellitus. Note: N is the total number of subjects

The higher event rate differences between the BVS and XIENCE groups associated with <2.25 mm RVD treatment were relatively more pronounced in subjects with diabetes mellitus (again most notable for rates of TLF, target vessel MI and stent thrombosis).

For comparison, the event rates in subjects *without* diabetes mellitus stratified by angiographic core lab-assessed RVD ≥2.25 mm or <2.25 mm are shown in Table 6.1-24.

Table 6.1-24. 1 Year Clinical Outcomes Stratified by Non-Diabetic Status and Core Laboratory-Assessed RVD – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	All Non-DM			All Non-DM with RVD ≥2.25 mm			All Non-DM with RVD <2.25 mm		
	BVS (N=904)	XIENCE (N=462)	Diff [95% CI][1]	BVS (N=748)	XIENCE (N=372	Diff [95% CI][1]	BVS (N=153)	XIENCE (N=88)	Diff [95% CI][1]
TLF	6.3% (57/900)	4.6% (21/457)	1.74% [-0.98%, 4.11%]	6.4% (48/745)	4.6% (17/368)	1.82% [-1.25%, 4.46%]	5.9% (9/152)	4.5% (4/88)	1.38% [-5.75%, 7.04%]
Cardiac Death	0.7% (6/900)	0.2% (1/457)	0.45% [-0.62%, 1.25%]	0.7% (5/745)	0.3% (1/368)	0.40% [-0.91%, 1.32%]	0.7% (1/152)	0.0% (0/88)	0.66% [-3.56%, 3.63%]
TV- MI	4.6% (41/900)	3.3% (15/457)	1.27% [-1.10%, 3.30%]	4.7% (35/745)	3.5% (13/368)	1.17% [-1.58%, 3.45%]	3.9% (6/152)	2.3% (2/88)	1.67% [-4.35%, 6.37%]
ID-TLR	1.8% (16/900)	2.0% (9/457)	-0.19% [-2.05%, 1.24%]	1.7% (13/745)	1.6% (6/368)	0.11% [-1.90%, 1.62%]	2.0% (3/152)	3.4% (3/88)	-1.44% [-7.71%, 2.86%]
Scaffold/ Stent Thrombosis	0.8% (7/894)	0.4% (2/456)	0.34% [-0.87%, 1.23%]	0.7% (5/739)	0.5% (2/367)	0.13% [-1.34%, 1.11%]	1.3% (2/152)	0.0% (0/88)	1.32% [-2.97%, 4.67%]

[1] Without multiplicity adjustment.
DM = diabetes mellitus. Note: N is the total number of subjects

FDA Comment: The Advisory Panel will be asked to consider whether or not the IFU should include additional language regarding an increased risk for adverse events when a BVS is implanted in a vessel with an angiographic core lab-assessed RVD <2.25 mm in patients with diabetes mellitus.

6.1.2.10 BVS Post-Dilatation

In ABSORB III, BVS post-dilatation was utilized at the discretion of the operator and was performed in 898 of 1385 (64.8%) lesions and not performed 487 of 1385 (35.2%) lesions. The rate of BVS clinical procure success was numerically lower when post-dilatation was performed, and post-dilatation did not appear to be associated with a consistent improvement in the 1-year rates of TLF, cardiac death, target vessel MI, ischemia-driven TLR, and stent thrombosis (Table 6.1-25).

Table 6.1-25. Comparison of Procedural Success and Event Rates between Post-Dilatation with Non-Compliant Balloon vs. Not Post-dilatation in the BVS Group

	Post-Dilatation With Non-Compliant Balloon (N=765)	Post-Dilatation Not Performed (N=454)
Clinical Device Success	94.7% (747/789)	94.8% (434/458)
Clinical Procedure Success	93.4% (708/758)	96.5% (437/453)
1-Year Rates		
TLF	8.1% (62/761)	7.5% (34/452)
Cardiac Death	0.8% (6/761)	0.4% (2/452)
Target Vessel MI	6.0% (46/761)	6.0% (27/452)
ID-TLR	3.2% (24/761)	3.3% (15/452)
Definite + Probable Scaffold/Stent Thrombosis	1.5% (11/751)	1.8% (8/451)

Note: ID-TLR = ischemia-driven target revascularization; N = the total number of subjects

In the subgroup of patients with an angiographic core lab assessed RVD of <2.25 mm, post–dilatation appeared to be associated with reduced rates of BVS and XIENCE stent thrombosis, with the observed benefit more pronounced in the BVS group (Table 6.1-26).

Table 6.1-26. 1 Year Stent/Scaffold Thrombosis of RVD < 2.25 mm Subgroup Stratified by Post-Dilatation Method – Per-Subject Analysis (Primary Analysis Group, ITT Population, Per Protocol MI Definition)

	ARC Definite + Probable Scaffold/Stent Thrombosis		
	BVS (N=242)	**XIENCE (N=133)**	**Difference [95% CI][1]**
RVD <2.25 mm Subgroup (All)	4.62% (11/238)	1.50% (2/133)	3.12% [-1.20%, 6.75%]
RVD <2.25 mm Subgroup without post-dilatation	8.11% (6/74)	2.53% (2/79)	5.58% [-2.02%, 14.25%]
RVD <2.25 mm Subgroup with ⩾1 post-dilatation	3.05% (5/164)	0.00% (0/54)	3.05% [-3.82%, 6.94%]
RVD <2.25 mm Subgroup with post-dilatation ⩾14 ATM	1.98% (2/101)	0.00 (0/36)	1.98% [-7.77%, 6.93%]

[1] Without multiplicity adjustment.

In the comparison of procedural success and event rates between post-dilatation with a non-compliant balloon vs. no post-dilatation, the data must be interpreted with caution. In ABSORB III, subjects were not randomized to post-dilatation versus no post-dilatation. The reasons for why an investigator decided to post-dilate a lesion could have been based on lesion complexity or technical issues during the index procedure. Therefore the clinical outcome of the analysis may not truly reflect the effect of post-dilatation when a BVS was used but rather the treatment conditions at the time of the index procedure.

The BVS IFU includes the following statement in the Precautions section:

> *Post-dilatation is strongly recommended for optimal scaffold apposition. When performed, post-dilatation should be at high pressure with a non-compliant balloon.*

FDA Comment: The Advisory Panel will be asked to address the statement in the Precautions section of the IFU regarding the strong recommendation for post-dilatation when implanting a BVS.

6.2 Additional BVS Studies Conducted Outside the US

Abbott Vascular has sponsored several clinical studies conducted outside of the United States, which provide additional, and for some studies, longer term data on the safety and effectiveness of the BVS. These studies are as follows:

1. ABSORB Cohort B
2. ABSORB EXTEND
3. ABSORB II RCT
4. ABSORB Japan RCT
5. ABSORB First

These studies have been briefly discussed in Section 4 (Regulatory History). Additional detail regarding design and results are provided in **Appendices 2-7**

6.2.1 Summary of Safety and Effectiveness Findings for BVS Use in Non-US Clinical Studies

Combining US and non-US studies, the number of BVS subjects and duration of follow-up is:

- 1 Year: 2836 BVS subjects (including 1322 subjects from ABSORB III)
- 2 Years: 1248 BVS subjects
- 3 Years: 735 BVS subjects
- 4 Years: 101 BVS subjects
- 5 Years: 101 BVS subjects

Table 6.2.1 shows summary clinical outcomes data and the longest available follow-up from the non-US BVS studies. It should be noted that the ABSORB Extend and ABSORB First studies allowed enrollment of subjects with complex clinical and lesion characteristics.

Table 6.2-1. Summary of Clinical Outcomes from non-US ABSORB Studies: ABSORB Cohort B (A-Cohort B), ABSORB Extend (A-Extend), ABSORB II, and ABSORB Japan including longest available follow-up

	A-Cohort B N=101	A-Extend N=812	ABSORB II		ABSORB Japan	
			BVS N=335	XIENCE N=166	BVS N=266	XIENCE N=134
1-Year						
TLF	6.9% (7/101)	5.1% (41/811)	4.8% (16/331)	3.0% (5/165)	4.2% (11/265)	3.8% (5/133)
CD	0.0% (0/101)	0.7% (6/811)	0.0% (0/331)	0.0% (0/165)	0.0% (0/265)	0.0% (0/133)
TVMI	3.0% (3/101)	3.3% (27/811)	4.2% (14/331)	1.2% (2/165)	3.4% (9/265)	2.3% (3/133)
ID-TLR	4.0% (4/101)	2.3% (19/811)	1.2% (4/331)	1.8% (3/165)	2.6% (7/265)	2.3% (3/133)
ST	0.0% (0/101)	1.0% (8/808)	0.9% (3/329)	0.0% (0/164)	1.5% (4/262)	1.5%(2/133)
2-Years						
TLF	9.0% (9/100)	6.9% (56/807)	7.0% (23/328)	3.0% (5/164)		
CD	0.0% (0/100)	1.1% (9/807)	0.6% (2/328)	0.0% (0/164)		
TVMI	3.0% (3/100)	4.2% (34/807)	5.2% (17/328)	1.2% (2/164)		
ID-TLR	6.0% (6/100)	4.1% (33/807)	2.7% (9/328)	1.8% (3/164)		
ST	0.0% (0/99)	1.5% (12/799)	1.5% (5/325)	0.0% (0/163)		
3-Years						
TLF	10.0% (10/100)	9.0% (55/613)				
CD	0.0% (0/100)	1.5% (9/613)				
TVMI	3.0% (3/100)	5.2% (32/613)				
ID-TLR	7.0% (7/100)	4.9% (30/613)				

	A-Cohort B N=101	A-Extend N=812	ABSORB II		ABSORB Japan	
			BVS N=335	XIENCE N=166	BVS N=266	XIENCE N=134
ST	0.0% (0/97)	2.0% (12/603)				
4-Years						
MACE	10.0 (10/100)					
CD	0.0% (0/100)					
TVMI	3.0% (3/100)					
ID-TLR	7.0% (7/100)					
ST	0.0% (0/95)					
5-Years						
MACE	11.0 (11/100)					
CD	0.0% (0/100)					
TVMI	3.0% (3/100)					
ID-TLR	8.0% (8/100)					
ST	0.0%(0/95)					

FDA Consideration: The Advisory Panel will be asked to consider whether or not the PMA includes adequate follow-up in a sufficient portion of the patient population identified in the proposed indications for use to confirm a reasonable assurance of BVS safety and effectiveness.

7 POST-APPROVAL STUDY (PAS)

The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues below are FDA's comments regarding potential post-approval studies, for the Panel to include in its deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has identified the following issues for which post-market data would be helpful:

- Long-term follow-up of the ABSORB III patient population.
- BVS performance in real-world use.
- The effectiveness of a new operator training program for optimal BVS use.
- The ability of operators to identify the appropriately sized coronary arteries for BVS implantation based on the labeled instructions for use.

In their written summary, Abbott Vascular has indicated that they plan on collaborating with FDA to construct a post-approval registry that will include approximately 2000-3000 subjects at approximately 150-200 sites. They state that the post-approval study will examine a broader subject population treated by a larger group of physician operators. The study will be designed to evaluate low frequency events, effectiveness of labeling, education for very small vessels (<2.5 mm), and confirm generalizability of the treatment with the BVS to real-world practice. The estimated follow-up of safety and effectiveness would be approximately 5 years.

FDA Comment: The Advisory Panel will be asked to provide recommendations on whether the sponsor's proposed post-approval commitments are acceptable or whether additional elements or objectives should be considered.

8 FDA Summary

The principal safety and effectiveness information for the Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System is derived primarily from the ABSORB III US pivotal clinical trial, in which 2008 subjects were randomized 2:1 to treatment with the BVS or the XIENCE stent. Additional BVS clinical data are available from other randomized and single arm studies conducted outside of the US, which provide patient follow-up beyond the 1-year ABSORB III data.

The Absorb III trial was a well-conducted and monitored study that provided appropriate levels of patient safety oversight. In Absorb III, the BVS met the primary endpoint of TLF at 1 year. The absolute difference in the 1-year TLF rate was 1.7% in favor of the XIENCE stent group (BVS 7.8% vs. XIENCE 6.1%). The upper bound of the corresponding 95% confidence interval was 3.93%, which was less than the pre-specified non-inferiority margin of 4.5%.

For the components of the TLF composite endpoint (cardiac death, target vessel MI, and ischemia-driven target lesion revascularization), event rates in the BVS group were numerically higher compared with the XIENCE group. In addition, the ARC definite plus probable stent thrombosis (ST) rate at 1-year in the BVS was >2-fold higher vs. the XIENCE group (1.54% vs. 0.74%, respectively). Although drawing conclusions from comparing event rates across different studies should be done with caution, the ABSORB III BVS ST rate exceeds the rates observed in contemporary trials involving currently approved, widely used metallic DES.

A post hoc analysis indicates that implanting a BVS in a vessel with a QCA-assessed reference vessel diameter (RVD) <2.25 mm was associated with an increased rate of cardiac events (TLF, target vessel MI) and stent thrombosis vs. a QCA-assessed RVD ≥2.25 mm. Further, the increased event rates associated with BVS use in small vessels was more pronounced in subjects with diabetes mellitus. However, for vessels with a QCA-assessed RVD ≥2.25 mm, cardiac event rates were lower relative to the rates in the overall ITT population.

Adjunctive imaging modalities that offer greater precision in vessel size assessment, such as online QCA, IVUS or OCT, were not required and were infrequently utilized in ABSORB III. The lower bound RVD inclusion criterion was 2.5 mm (visually assessed by the operator). Visual estimates of coronary artery dimensions often overestimate true vessel diameters. Although the precise overestimation of vessel diameters by visual assessment is not known, 0.25 mm is a reasonable approximation, such that a 2.50 mm visually estimated diameter correlates with a 2.25 mm QCA-measured diameter. In ABSORB III, scaffold or stent use in vessels smaller than the intended target vessel size was not uncommon; the angiographic core lab found that 19% of ITT subjects (18% and 20% of BVS and XIENCE subjects, respectively) underwent treatment of an artery <2.25 mm in diameter. Amongst vessels with an RVD <2.5, the median RVD was 2.08 mm in the BVS group and 2.1 mm in the XIENCE group.

For optimal angiographic and clinical outcomes with BVS use, appropriate vessel selection, pre-scaffold implantation lesion preparation, and (possibly) post-dilatation, appear to be particularly

important. Informative written instructions for use and training of new operators are required for safe and effective optimal BVS implantation.

The Panel's review and recommendations will help FDA decide whether, based on the currently available data, the BVS demonstrates a reasonable assurance of safety and effectiveness when used in accordance with the proposed indications.

Appendix 1

ABSORB III Lead-in Sub-Study

Objective: To evaluate the applicability and transferability of the didactic Absorb BVS physician training plan to US clinical practice in up to 50 subjects at up to 35 US sites.

Endpoints: None specified

Study Design: Prospective, single blind, open label, multicenter study. Enrollment of the lead-in phase occurred prior to the randomization phase of ABSORB III. The ABSORB III Lead-In subjects did not contribute to the ABSORB III trial endpoints.

Subjects: 24 subjects at 11 US sites**.**

Randomization: None

Key Inclusion/Exclusion Criteria: Eligibility criteria are the same as the ABSORB III Primary Analysis Group except for the following (since only a 3.0 x 18 mm BVS could be used):

- Lesion(s) must be located in a native coronary artery with RVD by visual estimation of ≥2.75 mm and ≤3.25 mm and lesion length by visual estimation of ≥8 mm and ≤14 mm.

PCI Treatment: Similar to the ABSORB III Primary Analysis Group.

Antiplatelet therapy: Identical to the Primary Analysis Group

Study sites and Enrollment: The first Lead-In subject was registered on December 28, 2012, and enrollment was completed on April 1, 2013 with a total of 24 subjects at 11 sites.

Follow-up: 30 and 180 days and 1, 2, 3, 4, and 5 years.

Statistical Hypotheses: None.

Results: The patient population was generally similar to the ABSORB III Primary Analysis Group. Subject demographics, risk factors, angiographic findings and key clinical outcomes are presented in tables A1-1 to A1-4.

Baseline Clinical Characteristics

Table A1-1. Key Baseline Subject Characteristics and Risk Factors – Per-Subject Analysis, Lead-In Population

	BVS (N=24)
Age (year)	63.1 ± 9.2 (24)
Male Subjects	62.5% (15/24)
Current Tobacco Use	33.3% (8/24)
Any Diabetes Mellitus (DM)	25.0% (6/24)
Hypertension	87.5% (21/24)
Dyslipidemia	95.8% (23/24)
Prior MI	20.8% (5/24)
Clinical Presentation	
Stable Angina	58.3% (14/24)
Unstable Angina	20.8% (5/24)
Silent Ischemia	20.8% (5/24)

Table A1-2. Key Angiographic Characteristics – Per-Subject Analysis, Lead-In Population

	BVS (N=24),(L=24)
Pre-Procedure QCA	
Lesion length, mm	12.58 ± 2.19 (24)
Reference vessel diameter, mm	2.76 ± 0.37 (24)
Minimal lumen diameter, mm	0.89 ± 0.22 (24)
%DS	67.03 ± 9.36 (24)
Post-Procedure QCA In-Device	
Minimal lumen diameter, mm	2.44 ± 0.27 (24)
% DS	12.26 ± 7.28 (24)
Post-Procedure QCA In-Segment	
Minimal lumen diameter, mm	2.17 ± 0.42 (24)
%DS	22.56 ± 10.33 (24)

N=number of subjects. L=number of lesions

Table A1-3. Clinical Outcomes Through 758 Days – Per-Subject Analysis, Lead-In Population, Per Protocol MI Definition

	BVS (N=24)
0-393 Days	
Target Lesion Failure	4.2% (1/24)
Cardiac Death	0.0% (0/24)
Target Vessel MI	4.2% (1/24)
ID-TLR	0.0% (0/24)
TVR	0.0% (0/24)
0-758 Days	
Target Lesion Failure	8.3% (2/24)
Cardiac Death	0.0% (0/24)
Target Vessel MI	8.3% (2/24)
ID-TLR	4.2% (1/24)
TVR	4.2% (1/24)

ID-TLR = ischemia-driven target revascularization; N = the total number of subjects

Table A1-4. Scaffold Thrombosis (Definite Plus Probable) Through 758 Days – Per-Subject Analysis, Lead-In Population

	BVS (N=24)
Acute Scaffold Thrombosis (≤ 1 day)	0.0% (0/24)
Acute/Subacute Scaffold Thrombosis (0 - 30 days)	0.0% (0/24)
Cumulative Scaffold Thrombosis through 393 Days (0 - 393 days)	0.0% (0/24)
Cumulative Scaffold Thrombosis through 758 Days (0 - 758 days)	4.17% (1/24)

Note: Scaffold Thrombosis = ARC definite + probable scaffold thrombosis. N = the total number of subjects

Appendix 2

ABSORB Pharmacokinetics (PK) Sub-Study

Objective: To determine the pharmacokinetics (PK) of everolimus delivered by the Absorb BVS in a non-randomized group of 12 subjects who only received Absorb BVS with a maximum of two *de novo* native coronary artery lesions after implantation. The ABSORB III PK subjects do not contribute to the ABSORB III primary endpoint rates.

Study Design: Prospective, open-label, unblinded sub-study at 2 clinical sites. Subjects received either one (N=8) or two (N=4) Absorb BVS with diameters of 2.5, 3.0 and 3.5 mm and lengths of 8, 12, 18 and 28 mm. The total everolimus dose ranged from 181 μg to 443 μg, depending on stent size (see Table A2-1 below).

Table A2-1 shows the total dose of everolimus on the various BVS diameters and lengths.

Table A2-1. Absorb BVS Sizes and Nominal Total Doses of Everolimus per Scaffold

BVS Diameter **(mm)**	**BVS Length (mm)**	**Drug Dose (μg)**
2.5, 3.0	8	76
2.5, 3.0	12	114
2.5, 3.0	18	181
2.5, 3.0	28	276
3.5	12	135
3.5	18	197
3.5	28	308

Inclusion and Exclusion Criteria: See ABSORB III enrollment criteria except for the following:

- All target lesions were to be treated with the Absorb BVS only
- Subjects in whom an Absorb BVS and a non-Absorb BVS device were implanted were excluded from the sub-study analysis and required to undergo the full 5-year follow-up.

Follow up schedule

- Blood Sampling Timing
    - Pre-Absorb BVS implantation: Baseline
        - Baseline was defined as prior to implantation of the first Absorb BVS on the day of the index procedure.
        - Post-Absorb BVS implantation: 10 and 30 minutes, 1 hr, 2 hrs, 4 hrs, 6 hrs , 12 hrs, 24 hrs (1 day), 48 hrs (2 days), 72 hrs (3 days), 96 hrs (4 days), 120 hrs (5 days), 168 hrs (7 days), 336 hrs (14 days), and 720 hrs (30 days).
- Clinical follow-up (either telephone contact or office visit unless otherwise noted) was required at the following: 30 ± 7 days; 180 ± 28 days; 1 year ± 28 days (office visit and ECG required); 2 years ± 28 days; 3 years ± 28 days; 4 years ± 28 days; and 5 years ± 28 days.

Results: PK sub-study participants were generally comparable to the characteristics of the population of the ABSORB III Primary Analysis Group but with some differences due to the small size of the PK Study group. PK sub-study had:

- More male subjects (91.7% vs 70.5%)
- More subjects with dyslipidemia (100.0 vs. 76.8%) and hypertension (100.0 vs. 80.9%)

requiring medication
- More subjects with stable angina (75.0 vs. 58.5%)
- Fewer subjects who had undergone prior coronary intervention (9.1% vs. 38.5%)

Overall, the baseline target lesion characteristics and post-procedure target lesion measurements were comparable between the PK sub-study and ABSORB III Primary Analysis Group subjects including minimal differences in percent diameter stenosis (67.07 vs 65.47), Eccentricity (83.3 vs. 75.8%), Calcification (33.3 vs. 32.8%) and lesion length (12.21 vs 12.77%).

The everolimus whole blood concentration-time curves are shown Figure A1-1.

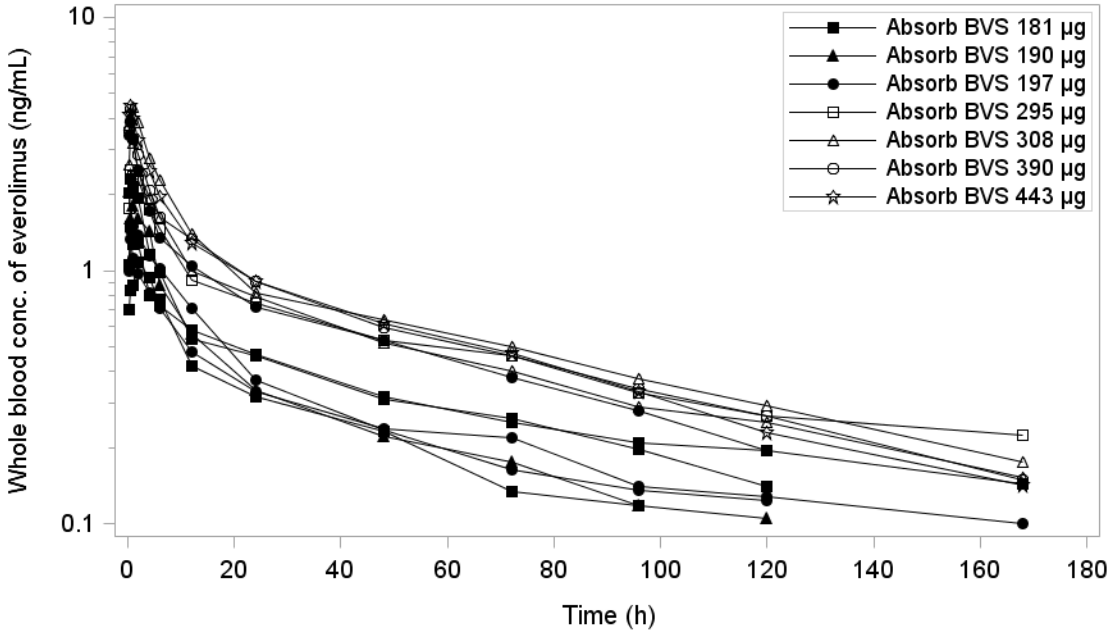


Figure A2-1. **Whole Blood Concentration-Time Curves of Everolimus**

Key Outcomes

- Everolimus blood concentrations increased rapidly after the scaffold deployment, reaching maximum concentrations between 0.17 and 2.37 hours (t_{max}).
- The everolimus concentrations declined thereafter with a terminal half-life ranging between 45.9 and 115 hours, with no obvious trend with dose.
- Everolimus blood concentrations were low but measurable up to 168 hours (7 days) after the last scaffold was implanted.
- Systemic exposure of everolimus, measured by C_{max} and AUC, increased with the total scaffold dose (ranging from 181 – 443 µg). The C_{max} values ranged from 1.085 – 4.460 ng/mL. Dose-normalized C_{max} and area under the everolimus concentration vs. time curve (AUC) were comparable across the total scaffold dose, with a relatively low inter-individual variability in everolimus exposure after Absorb BVS deployment (for dose-normalized C_{max}, AUC_{24h}, AUC_{last}, $AUC_{0-\infty}$, %CV was 35.6%, 25.7%, 26.2% and 23.3%, respectively).
- Formal statistical testing was done to assess dose proportionality. The slope of the correlation line between dose-normalized C_{max}, AUC_{24h}, AUC_{last}, and $AUC_{0-\infty}$, and dose were not statistically different from zero, indicating a dose proportional increase in concentrations.

- Due to the proportional increase with the loaded dose (determined by the Absorb BVS size), everolimus concentrations are very predictable for various scaffold sizes and number of implanted Absorb BVS.

The results of the ABSORB Pharmacokinetics sub-study are consistent with those found with the approved XIENCE V stent, where everolimus blood concentrations increased rapidly after implantation and then declined exponentially over a period of 7 days.

Appendix 3

Summaries of Other Clinical Studies Conducted Outside the US: ABSORB Cohort B

Objective: Exploratory/feasibility study to test the performance of the BVS System (ABSORB Cohort B device) in the treatment of single *de novo* native coronary artery lesion.

Key Endpoints

- Acute success
- Major Adverse Cardiac Event(MACE) and Target Vessel Failure (TVF) at each follow-up
- In-device and in-segment late loss at 6 months and 2 years,
- In-device and in-segment Angiographic Binary Restenosis (ABR) rate at 6 months and 2 years by QCA
- In-device mean and minimal lumen area at 6 months and 2 years by IVUS
- Descriptive analysis of vascular and stent morphology obtained with MSCT at 18 months and 5 years.

Design: A prospective, open-labeled, multi-center study

Subjects: One hundred and one (101) enrolled subjects were divided between two groups: Group 1, n=45 (imaging follow-up at 180 days and 2 years) and Group 2, n=56 (imaging follow-up at 1 year and 3 years). All subjects in Cohort B received a single 3.0 x 18 mm BVS Cohort B device per lesion treated.

Randomization: None

Key Inclusion Criteria

- Evidence of myocardial ischemia (stable or unstable angina, or silent ischemia).
- up to two *de novo* native coronary artery lesions in separate epicardial vessels with visually estimated nominal vessel diameters of 3.0 mm and lesion(s) length ≤14 mm e.
- Percent diameter stenosis (%DS) ≥50% and <100%; TIMI flow of ≥1.

Key Exclusion Criteria: Aorto-ostial location; left main location within 2 mm of the origin of the LAD or LCX; excessive tortuosity; extreme angulation (≥90°); heavy calcification; restenotic from previous intervention; target vessel containing thrombus; other clinically significant lesions in the target vessel or side branch

PCI Treatment:

- Pre-dilatation of the target lesion mandatory.
- Target lesions measured ≤ 14 mm in length by visual estimation were treated with a 3.0 x 12 mm or 3.0 x 18 mm Absorb BVS.
- It was recommended to cover 2 mm of non-diseased tissue on either side of the BVS.
- The target lesion had to be treated with single BVS, and planned overlapping was not allowed.
- Bailout procedures could be performed with a XIENCE V Stent or a Cypher Stent (if XIENCE V was not available).
- Post-dilatation was performed at operator discretion, but only using balloons sized to fit within the boundaries of the BVS.

Antiplatelet therapy

- Pre-Procedure: Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of clopidogrel ≥300 mg and aspirin ≥300 mg 6 to 72 hours prior to the index procedure, but no later than 1 hour after the procedure.
- Post-Procedure: All subjects were to be maintained on 75 mg clopidogrel daily for a minimum of 6 months and ≥75 mg of aspirin daily for the length of the clinical investigation (5 years).

Study Sites and Dates of Enrollment: A total of 101 subjects were enrolled at 12 clinical sites located in Europe, Australia, and New Zealand between March 19, 2009 and November 6, 2009. This study is now completed.

Follow up schedule: Subjects were evaluated at 30 days, 180 days, 270 days, 12 months, 18 months (subset), 2 years, 3 years, 4 years and 5 years. Group 1 subjects had invasive imaging with qualitative coronary angiography, IVUS, IVUS-Virtual Histology, and OCT at 6 months, 2 years and 5 years. Group 2 subjects had invasive imaging at 12 months, 3 years and 5 years. Vasomotor function test using nitroglycerin was performed at 2, 3 and 5 years. A Multi-slice CT (MSCT) scan was mandatory for subset of subjects at 18 months and at 5 years.

Statistical Hypotheses: None

Results

- **Study Population:** The mean age was 62.26 ± 8.93 years. 72.3% were men, 17.0% current smokers, 16.8% diabetics, 66.0% had hypertension, 85.1% had hypercholesterolemia, 25.0% had prior MI, 6.9% had a prior target vessel cardiac intervention, 14.9% presented with unstable angina, and 20.8% had multi-vessel disease.
- **Baseline Angiographic Parameters:** There were 40% type B2 and 4% type C lesions. Based on QCA, the mean lesion length was 9.92 ± 3.65 mm and the mean RVD was 2.61 ± 0.37 mm. Pre-procedure MLD was 1.06 ± 0.28 mm and the mean %DS was 58.99 ± 10.00%.

The key clinical results are presented in Table A3-1, and the key imaging and vasomotion study results are shown in Tables A3-2 through A3-7.

Table A3-1. Key Clinical Outcomes of ABSORB Cohort B (ITT Population) through 5 years

	30 days (N=101)	6 months (N=101)	1 year (N=101)	2 year (N=100*)	3 year (N=100*)	4 year (N=100*)	5 year (N=100*)
COMPOSITE EFFICACY AND SAFETY							
MACE	2.0% (2/101)	5.0% (5/101)	6.9% (7/101)	9.0% (9/100)	10.0% (10/100)	10.0 (10/100)	11.0 (11/100)
EFFICACY							
Ischemia-Driven TLR	0.0% (0/101)	2.0% (2/101)	4.0% (4/101)	6.0% (6/100)	7.0% (7/100)	7.0% (7/100)	8.0% (8/100)
TLR, CABG	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
TLR, PCI	0.0% (0/101)	2.0% (0/101)	4.0% (4/101)	6.0% (6/100)	7.0% (7/100)	7.0% (7/100)	8.0% (8/100)
Ischemia-Driven TVR	0.0% (0/101)	2.0% (2/101)	4.0% (4/101)	8.0% (8/100)	10.0% (10/100)	10.0% (10/100)	11.0% (11/100)
SAFETY							
Cardiac Death	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
All MI	2.0% (2/101)	3.0% (3/101)	3.0% (3/101)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)
QMI	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)	0.0% (0/100)
NQMI	2.0% (2/101)	3.0% (3/101)	3.0% (3/101)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)	3.0% (3/100)
Scaffold Thrombosis	0.0% (0/101)	0.0% (0/101)	0.0% (0/101)	0.0% (0/95)	0.0% (0/95)	0.0% (0/95)	0.0% (0/95)

* One subject lost to follow-up at 2-year follow-up.
Note: MACE: Cardiac death, MI, ischemia-driven TLR. .
Note: MI adjudicated per the WHO definition: Development of new, pathological Q wave on the ECG or elevation of CK to ≥2 times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.

Intravascular Ultrasound (IVUS) Outcomes (Tables A3-2 and A3-3)

Table A3-2. Paired IVUS Results at Post-procedure, 6 Months, 2 Years, and 5 Years (Group 1, ITT Population)

Group 1 IVUS (paired)	Time Point				P-values* (Paired Analysis)		
	Post-Proc (L = 21)	6-Month (L = 21)	2-Year (L = 21)	5-Year (L = 21)	Post vs. 6M	6M vs. 2Y	2Y vs. 5Y
Vessel Area (mm^2)	14.56 ± 3.82	14.92 ± 3.78	15.88 ± 4.02	15.28 ± 4.53	0.0957	0.0009	0.0785
Scaffold Area (mm^2)	6.75 ± 1.19	6.63 ± 1.16	7.52 ± 1.79	N/A	0.1754	< 0.0001	N/A
Lumen Area (mm^2)	6.75 ± 1.19	6.59 ± 1.20	7.24 ± 1.91	7.46 ± 2.45	0.0850	0.0153	0.2774
Lumen AS (%)	16.91 ± 3.82	20.12 ± 7.99	25.08 ± 8.81	34.43 ± 11.10	0.1157	0.0136	0.0001
Plaque Area (mm^2)	7.81 ± 2.98	8.33 ± 2.88	8.64 ± 2.85	7.75 ± 2.62	0.0140	0.0696	0.0005
NIH Area (mm2)		0.07 ± 0.12	0.31 ± 0.30	NM	-	0.0008	-
Area Obstruction (%)		1.16 ± 2.06	4.56 ± 4.60	NM	-	0.0006	-

*The presented p values are not based on pre-specified hypothesis tests and without multiplicity adjustment.
Note: Data are presented as Mean ± SD. AS=Area Stenosis, Post-Proc=Post-Procedure. L is the number of lesions with a paired measurement for the specific variable.

Table A3-3. Paired IVUS Results at Post-procedure, 1 year, 3 Years, and 5 Years (Group 2, ITT Population) – Paired Analysis

Group 2 IVUS (paired)	Time Point				P-values* (Paired Analysis)		
	Post-Proc. (L=30)	12 months (L=30)	3 years (L=30)	5 years (L=33)	Post vs. 12M	12M vs 3Y	3Y vs. 5Y
Vessel Area (mm^2)	13.61 ± 2.40	14.15 ± 2.61	14.25 ± 2.57	13.23 ± 2.70	0.063	0.456	0.0003
Scaffold Area (mm^2)	6.31 ± 0.86	6.37 ± 0.97	7.05 ± 1.39	NM	0.865	<0.0001	-
Lumen Area (mm^2)	6.31 ± 0.86	6.31 ± 1.01	6.70 ± 1.48	6.48 ± 1.50	0.420	0.003	0.184
Lumen AS (%)	20.01 ± 6.09	21.63 ± 6.92	25.29 ± 9.39	25.67 ± 8.60	0.567	0.016	0.436
Plaque Area (mm^2)	7.30 ± 1.85	7.84 ± 1.92	7.55 ± 1.58	6.79 ± 1.90	0.010	0.051	0.0001
NIH Area (mm^2)	-	0.09 ± 0.14	0.35 ± 0.48	NM	-	<0.0001	-
Area Obstruction (%)	-	1.39 ± 2.27	5.22 ± 7.64	NM	-	0.0002	-

AS=Area Stenosis; NIH= Neointimal Hyperplasia, NM=Not Measurable, N=number of subjects, L=Number of lesions, Post-Proc=Post-Procedure.

* The presented p values are not based on pre-specified hypothesis tests and without multiplicity adjustment.

Optical Coherence Tomography (OCT) Analysis (Tables A3-4 and A3-5)

Table A3-4. Paired OCT Results at Post-procedure, 6 Months, 2 and 5 Years (Group 1, ITT Population)

Group 1 OCT (paired)	Time Point				P-values* (Paired Analysis)			
	Post-Proc (L = 13)	6-Month (L = 13)	2-Year (L = 13)	5-Year (L = 13)	Post vs. 6M*	6M vs. 2Y*	Post vs. 2Y*	2Y vs. 5Y*
Lumen Area (mm^2)	7.28 ± 1.24	6.04 ± 1.20	6.17 ± 1.44	6.38 ± 1.47	0.0002	0.8926	0.0081	0.3054
Min. Lumen Area (mm^2)	5.82 ± 0.96	4.51 ± 1.28	4.21 ± 1.25	3.65 ± 1.39	0.0007	0.1677	0.0012	0.3396
Scaffold Area (mm^2)	7.55 ± 1.17	7.79 ± 1.20	8.54 ± 1.71	NM	0.2163	0.1909	0.0171	
Min Scaffold Area (mm2)	6.18 ± 1.08	6.21 ± 1.31	6.44 ± 1.20	NM	0.8394	0.5879	0.6848	
NIH Area (mm^2)	N/A	1.53 ± 0.36	2.22 ± 0.47	N/A	N/A	0.0012	N/A	
% Luminal AS	19.82 ± 5.98	25.98 ± 11.48	31.60 ± 13.37	42.40 ± 18.08	0.1099	0.0398	0.0061	0.0574
Strut Core Area (mm^2)	0.22 ± 0.03	0.22 ± 0.06	0.15 ± 0.02	N/A	0.8926	0.0012	0.0002	
% Uncovered Struts	96.97 ± 6.83	1.80 ± 1.63	1.40 ± 2.37	N/A	0.0002	0.1909	0.0002	

* The presented p values are not based on pre-specified hypothesis tests and without multiplicity adjustment.

Note: Data are presented as Mean ± SD or %. L is the number of lesions with a paired measurement for the specific variable. AS=Area Stenosis, NIH= Neointimal Hyperplasia, Min Scaffold Area=Minimal Scaffold Area, NM=Not Measureable, Post-Proc=Post-Procedure.

Table A3-5. Paired OCT Results at Post-procedure, 1, 3 and 5 Years (Group 2, ITT Population)

Group 2 OCT (paired)	Time Point				P-values (Paired Analysis)			
	Post-Proc. (L=17)	1 Year (L=17)	3 years (L=17)	5 years (L=17)	Post vs. 1Y*	1Y. vs 3Y*	Post vs. 3Y*	3Y vs. 5Y*
Lumen Area (mm^2)	7.54 ± 0.88	5.94 ± 1.29	6.01 ± 1.49	5.93 ± 1.53	0.0011	0.6777	0.0013	0.4954
Min. Lumen Area (mm^2)	6.14 ± 0.94	4.35 ± 1.09	4.34 ± 1.48	4.12 ± 1.38	< 0.0001	0.8266	< 0.0001	0.1167
Scaffold Area (mm^2)	7.61 ± 0.83	7.45 ± 0.84	8.61 ± 1.98	NM	0.2435	0.0003	0.0305	-
Min Scaffold Area (mm^2)	6.27 ± 0.84	5.95 ± 0.91	6.66 ± 1.58	NM	0.1556	0.0267	0.2788	-
NIH Area (mm^2)	-	1.42 ± 0.71	2.39 ± 0.68	NM	-	< 0.0001	-	-
% Luminal AS	18.77 ± 6.01	27.17 ± 9.25	29.03 ± 15.46	31.43 ± 12.45	0.0056	0.8900	0.0448	0.1928
Strut Core Area (mm^2)	0.19 ± 0.03	0.16 ± 0.02	0.20 ± 0.03	NM	0.0079	0.0002	0.4307	-
% Uncovered Struts	97.65 ± 5.56	3.03 ± 2.81	1.70 ± 1.59	NM	< 0.0001	0.0131	< 0.0001	-

* The presented p values are not based on pre-specified hypothesis tests and without multiplicity adjustment.
Note: L=Number of lesions. AS=Area Stenosis, Min Scaffold Area=Minimal Scaffold Area, NIH= Neointimal Hyperplasia, NM=Not Measureable, Post-Proc=Post-Procedure.

Multi-Slice Computed Tomography (MSCT) Analysis (Table A3-6)

Table A3-6. MSCT Analysis (ITT Population)

	18 Months (L = 61)
Mean Vessel Area (mm^2)	14.09 ± 4.29
Mean Lumen Area (mm^2)	5.15 ± 1.35
Mean Plaque Area (mm^2)	8.94 ± 3.41
Area Stenosis (%)	22.73 ± 22.41

L=Number of lesions.

Vasomotor Function (Table A3-7)

Table A3-7. Vasomotor Function by Nitroglycerine Injection at 2, 3 and 5 years (PTE Population)

	Mean Luminal Diameter (mm)						p-values*, Pre vs. Post		
	Group B1 2 Y (L = 33)		Group B2 3 Y (L = 47)		Full Cohort 5 Y (L = 57)		2Y	3Y	5Y
	Pre-NTG	Post-NTG	Pre-NTG	Post-NTG	Pre-NTG	Post-NTG			
Proximal	2.48 ± 0.46	2.65 ± 0.42	2.51 ± 0.39	2.63 ± 0.48	2.53 ± 0.44	2.64 ± 0.43	0.0018	0.0065	<0.0001
Distal	2.26 ± 0.41	2.40 ± 0.40	2.28 ± 0.33	2.41 ± 0.35	2.26 ± 0.41	2.39 ± 0.39	0.0002	<0.0001	<0.0001
Scaffold	2.44 ± 0.37	2.47 ± 0.35	2.45 ± 0.37	2.50 ± 0.39	2.48 ± 0.38	2.56 ± 0.37	0.0352	0.0050	<0.0001

* The presented p values are not based on pre-specified hypothesis tests and without multiplicity adjustment.
Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Summary of Results

- The late lumen loss of 0.18 mm at 6 months for Group 1 and 0.27 mm at 1 year for Group 2 were lower than the earlier generation Absorb Cohort A scaffold.
- The 5 year MACE rate was 11%, and there were no cardiac deaths or BVS thrombosis

events.

- Serial IVUS and OCT studies demonstrated late lumen enlargement and an increase in BVS area at 2 years (Group 1) and at 3 years (Group 2), but there were some inconsistencies in measurement trends between imaging modalities (IVUS vs. OCT) and between Groups 1 and 2 at 5 years.
- Serial OCT results showed continuous resorption of the scaffold struts over time with complete resorption observed at 5-years.
- Vasomotor function, as demonstrated by increase in lumen diameter post-nitrate infusion, was detected at 3 and 5 years.
- Non-invasive MSCT imaging appeared to be feasible. MSCT at 18 months in 61 lesions treated with the BVS demonstrated a mean lumen area of 5.15 ± 1.35 mm^2 and a mean area stenosis of $22.7 \pm 22.4\%$.

Appendix 4

Summaries of Other Clinical Studies Conducted Outside the US: ABSORB EXTEND

Objective: The ABSORB EXTEND Study is a global continued access registry designed to provide BVS experience in different geographies with broad inclusion criteria including the treatment of multi-vessel disease and longer lesions with either a longer length BVS or overlapping scaffolds.

Key Clinical Endpoints

- Acute procedure success
- Major adverse cardiac events (MACE), target lesion failure, and target vessel failure.

Design: A prospective, single-arm, open-label clinical study

Randomization: None

Key Inclusion/Exclusion Criteria

- Evidence of myocardial ischemia (stable or unstable angina, or silent ischemia).
- Target vessel diameter (D_{max}) of ≥2.0 mm and ≤3.3 mm by on-line QCA or IVUS, lesion length ≤28 mm, percent diameter stenosis of ≥50% and <100%, and TIMI flow of ≥1.
- Maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels.
- Key angiographic exclusion criteria included: aorto-ostial location; left main location; lesion within 2 mm of the origin of the LAD or LCX; excessive tortuosity; extreme angulation (≥90°); heavy calcification; myocardial bridging; restenosis from previous intervention; target vessel containing thrombus; or other clinically significant lesions in the target vessel or side branch.

PCI Treatment:

- Pre-dilatation of the target lesion mandatory.
- On-line QCA or IVUS was required for the assessment of target vessel diameter for appropriate BVS size selection.
- Four sizes of the Absorb BVS, 2.5 mm x 18 mm, 2.5 mm x 28 mm, 3.0 mm x 18 mm, and 3.0 mm x 28 mm, were available for the study.
- Target lesions measured ≤22 mm in length were treated with a single BVS, while the target lesion measure >22 mm and ≤ 28 mm was treated by overlapping of two BVS. Overlap length had to be a minimum of 1 mm and a maximum of 4 mm.
- It was recommended to cover 2 mm of non-diseased tissue on either side of the BVS.
- Bailout procedures could be performed with a commercial everolimus-eluting stent (*e.g.*, XIENCE) or an Absorb BVS of appropriate length.
- Post-dilatation was performed at operator discretion using balloons sized to fit within the boundaries of the BVS.

Antiplatelet therapy:

- Pre-procedure: Subjects who were not on chronic antiplatelet or aspirin therapy received a loading dose of a thienopyridine (≥300 mg of clopidogrel, ≥60 mg of prasugrel, or 180 mg of ticagrelor) and aspirin (≥300 mg) 6 to 72 hours prior to the index procedure, but no later

than 1 hour after the procedure.

- **Post-Procedure:** All patients were to be maintained on 75 mg clopidogrel daily, 10 mg of prasugrel daily, or 90 mg twice daily of ticagrelor for a minimum of 6 months and ≥75 mg of aspirin daily for the length of the clinical investigation.

Study site and dates of enrollment: 812 subjects at 56 sites (Europe, Asia-Pacific, Latin America, and Canada) were enrolled between January 11, 2010 and October 2, 2013. At the time of the latest database lock (January 21, 2015), all subjects have completed 1-year follow-up and 807 subjects and 613 subjects have been completed 2 and 3-years follow-up, respectively.

Follow up schedule: Subjects evaluated at 30 days, 180 days, 12 months, 18 months (subset), 2 years and 3 years.

Statistical Analyses: No hypothesis testing. The presented clinical results are based on the ITT population.

RESULTS

- **Study Population:** The mean age was 61.12 ± 10.75 years, and 74.3% (603/812) were male, 23.2% (188/812) were tobacco users, 69.3% (563/812) had hypertension, 67.7% (550/812) had dyslipidemia, 28.5% (230/807) had prior MI, 26.5% (215/812) had diabetes.
- **Accountability of Subjects:** A total of 874 lesions were treated in 812 subjects, with 7.6% (62/812) of the subjects having two target lesions treated and 10.5% (85/812) having long lesions treated with planned overlapping BVS. Table A4-1 shows clinical outcomes data for all 812 subjects at one year, with key safety and effectiveness outcomes also presented for years 2 and 3; year 3 data are available for 613 subjects.

The ABSORB EXTEND clinical results are shown in Tables A4-1 and A4-2.

Table A4-1: ABSORB EXTEND: Acute Success (BVS N= 812; L=874)

Clinical Device Success - Per Lesion	98.9% (861/871)
Clinical Procedure Success - Per Subject	97.0% (785/809)

Note: N is the total number of subjects, L is the total number of target lesions.

Table A4-2. ABSORB EXTEND Clinical Results (ITT population) – 1-3 Year Results

	1 Year (N=812)	2 Years (N=807)	3 years (N=613)
TLF	5.1% (41/811)	6.9% (56/807)	9.0% (55/613)
EFFECTIVENESS			
Ischemia-Driven TLR	2.3% (19/811)	4.1% (33/807)	
Ischemia-Driven TVR	2.8% (23/811)		
SAFETY			
All Death	1.1% (9/811)		
Cardiac Death	0.7% (6/811)	1.1% (9/807)	1.5% (9/613)
Vascular Death	0.1% (1/811)		
Non-cardiovascular death	0.2% (2/811)		
TV-MI	3.3% (27/811)	4.2% (34/807)	5.2% (32/613)
QMI	1.0% (8/811)		
NQMI	2.3% (19/811)		
All MI	3.3% (27/811)		
QMI	1.0% (8/811)		
NQMI	2.3% (19/811)		
Cumulative ARC-defined Def + Prob Scaffold Thrombosis	1.0% (8/808)	1.5%(12/799)	2.0% (12/603)
Acute (< 1 day)	0.0% (0/812)		
Sub-Acute (1-30 days)	0.6% (5/812)		
Late (31-365 days)	0.4% (3/806)		

Note: MI adjudicated per the WHO definition: Development of new, pathological Q wave on the ECG or elevation of CK to ≥2 times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.

Summary of Results

- TVF and MACE rates at 1 year were 5.5% and 5.0%, respectively.
- There was no acute ST reported.
- The definite/probable sub-acute, late, and very late (366-758 days) ST rates were 0.6%, 0.4% and 0.5%, respectively.
- The ARC definite plus probable scaffold thrombosis rates were 1.0%, 1.5%, and 2.0% at 1, 2, and 3 years, respectively.

Appendix 5

Summaries of Other Clinical Studies Conducted Outside the US: ABSORB II Randomized Clinical Trial

Objective: A CE mark post-approval randomized trial designed to compare the safety, effectiveness, and performance of the BVS compared to the XIENCE family of DES in the treatment of *de novo* native coronary artery lesions.

Co-Primary Endpoints

- Vasomotor function assessed by the change in mean lumen diameter between pre- and post-nitrate at 3 years
- Angiographic minimum lumen diameter change from post-procedure to 3 years follow-up

Major Secondary Endpoint: IVUS-assessed in-scaffold/in-stent mean lumen area change from post-procedure to 3 years follow-up

Other Endpoints

- Cardiac events including target lesion failure, all death, cardiac death, MI, and repeat revascularization.
- Angiographic and IVUS measurements post-procedure and at 3 years follow-up.
- Multi-slice CT assessment of vascular and BVS morphology and quantitative measurement of the treated segment at 3 years.
- Quality of life assessment pre-procedure, at 180 days, and annually through 5 years using the SF-12 Health Survey, the EuroQoL 5D (EQ-5D), and the Seattle Angina Questionnaire (SAQ).

Design: A prospective, randomized, active-controlled, single-blinded, multicenter trial

Randomization: Subjects were randomly assigned to receive either the BVS or a XIENCE stent in a 2:1 ratio. Randomization was stratified by diabetes mellitus status and number of planned target lesions.

Key Inclusion and Exclusion Criteria

- Evidence of myocardial ischemia.
- Up to 2 *de novo* native coronary artery target lesions, each located in different major epicardial vessels.
- Angiographic D_{max} between 2.25 mm and 3.8 mm estimated by on-line QCA and a lesion length ≤48 mm.
- Percent diameter stenosis ≥50% and <100% with TIMI flow ≥1.
- Key angiographic exclusion criteria included: aorto-ostial location; left main location; location within 2 mm of the origin of the LAD or LCX; excessive tortuosity (≥ two 45° angles); extreme angulation (≥ 90°); heavy calcification proximal to or within the target lesion; myocardial bridge; restenotic lesion; target vessel containing thrombus; and bifurcation lesions with side branch ≥2 mm in diameter or with a side branch <2 mm in diameter requiring guide wire protection or dilatation.

PCI Treatment:

- On-line QCA or IVUS was required for the assessment of target vessel diameter for appropriate BVS size selection
- Mandatory target lesion pre-dilatation with a balloon 0.5 mm smaller in diameter than the planned study device.
- Planned overlapping of study devices allowed for long lesion treatment.

Antiplatelet therapy:

- **Pre-procedure:** Loading dose of aspirin (250-500 mg) and an ADP antagonist (300-600 mg of clopidogrel or 60 mg of prasugrel) 0 to 72 hours prior to the index procedure or 1 hour after the end of the procedure.
- **Post-procedure:** All subjects maintained on an ADP antagonist (≥75 mg of clopidogrel, ≥10 mg of prasugrel, or ≥90 mg ticagrelor twice daily) for a minimum of 180 days and aspirin (≥75 mg) for 5 years following the index procedure.

Study site and dates of enrollment: Between Nov 28th, 2011 and June 4th, 2013, 501 subjects from 46 investigational sites in Europe and New Zealand were registered and randomly assigned to the BVS group (335 subjects) or the XIENCE group (166 subjects).

Follow up schedule: Clinical follow-up at 30 days, 180 days and at 1, 2, 3, 4 and 5 years. All subjects undergo coronary angiography, IVUS (gray-scale and IVUS-Virtual Histology) pre- and post-device implantation and at 3-year follow-up. A Multi Slice Computed Tomography (MSCT) scan will be performed in BVS subjects at 3 years follow-up.

Statistical Analyses:

- Vasomotor function will be tested for superiority
- Minimum lumen diameter change will be tested for non-inferiority (non-inferiority margin of 0.14 mm). If non-inferiority is met with higher value in the BVS arm, then superiority will be tested.
- Analyses of secondary endpoints are descriptive.

Results

- **Study Population Demographics:** The mean age was 61.5 ± 10.0 and 60.9 ± 10.0 years in the BVS arm and XIENCE arms respectively. The patient population consisted of predominately males, 75.5% in the Absorb arm and 79.5% in the XIENCE arm. There was a high prevalence of hypertension (69.0% vs. 71.7%) and dyslipidemia (75.2% vs. 80.1%) in the BVS group vs. the XIENCE group, respectively. Over 20% of the population was diabetic (23.9% vs. 24.1% for the BVS and XIENCE arms, respectively).
- **Accountability of Subjects:** A total of 364 lesions were treated in 335 BVS subjects and 182 lesions in 166 XIENCE subjects. Early termination at 1 year, due to consent withdrawal or death, affected 1.8% (6/335) of the subjects in the BVS group and 1.2% (2/166) in the XIENCE group. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

Safety and Effectiveness

The 1-year safety and effectiveness results are presented in Table A5-1. These analyses are based on the ITT population. No subjects have reached the 3-year follow-up primary imaging endpoints.

Table A5-1. ABSORB II Clinical Results (ITT Population) – 1 Year Results

	BVS (N = 335)	XIENCE (N = 166)	Difference [95% CI][1]
***TLF**	4.8% (16/331)	3.0% (5/165)	1.80% [-2.48%, 5.16%]
Effectiveness			
Ischemia-Driven TLR	1.2% (4/331)	1.8% (3/165)	-0.61% [-4.08%, 1.60%]
Ischemia-Driven TVR	1.8% (6/331)	3.6% (6/165)	-1.82% [-6.01%, 1.04%]
SAFETY			
All Death	0.0% (0/331)	0.6% (1/165)	-0.61% [-3.35%, 0.65%]
Cardiac Death	0.0% (0/331)	0.0% (0/165)	0.00% [N/A]
Vascular Death	0.0% (0/331)	0.0% (0/165)	0.00% [N/A]
Non-cardiovascular Death	0.0% (0/331)	0.6% (1/165)	-0.61% [-3.35%, 0.65%]
**TV-MI	4.2% (14/331)	1.2% (2/165)	3.02% [-0.51%, 5.90%]
QMI	0.6% (2/331)	0.0% (0/165)	0.60% [-1.71%, 2.18%]
NQMI	3.6% (12/331)	1.2% (2/165)	2.41% [-1.05%, 5.16%]
All MI	4.5% (15/331)	1.2% (2/165)	3.32% [-0.25%, 6.26%]
QMI	0.6% (2/331)	0.0% (0/165)	0.60% [-1.71%, 2.18%]
NQMI	3.9% (13/331)	1.2% (2/165)	2.72% [-0.78%, 5.53%]
Cardiac Death or MI	4.5% (15/331)	1.2% (2/165)	3.32% [-0.25%, 6.26%]
ARC-defined Definite + Probable Scaffold/Stent Thrombosis (0-393 days)	0.9% (3/329)	0.0% (0/164)	0.91% [-1.45%, 2.65%]
Acute (≤ 1 day)	0.3% (1/335)	0.0% (0/166)	0.30% [-1.98%, 1.67%]
Sub-Acute (> 1-30 days)	0.3% (1/334)	0.0% (0/166)	0.30% [-1.98%, 1.68%]
Late (31-365 days)	0.3% (1/329)	0.0% (0/164)	0.30% [-2.00%, 1.70%]
Very Late (> 365-393 days)	0.0% (0/329)	0.0% (0/164)	0.00% [N/A]

[1] Without multiplicity adjustment. Note: 1-year timeframe includes a window of ± 28 days.
Note: MI is per protocol definition:

- Q wave MI :Development of new, pathological Q wave on the ECG.
- Non-Q wave MI: Elevation of CK levels to ≥2 times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.

Summary of the 1-Year Clinical Results:

- The TLF rate was 4.8% in the BVS group and 3.0% in the XIENCE group.
- The TLF rate using the ABSORB III per protocol MI definition was 6.0% for BVS vs. 4.2% for XIENCE
    - The target vessel MI rate was 5.4% for BVS vs. 2.4% for XIENCE
- The cumulative (0-393 days) rate of ARC definite + probable scaffold/stent thrombosis was 0.9% (3/329) in the BVS group vs. 0.0% (0/164) in the XIENCE group.

Appendix 6

Summaries of Other Clinical Studies Conducted Outside the US: ABSORB Japan Randomized Controlled Trial

Objective: To evaluate the safety and effectiveness of the BVS in the treatment of subjects with ischemic heart disease caused by *de novo* native coronary artery lesions in a Japanese population vs. the XIENCE family of DES.

Primary Endpoint: TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year.

Secondary Endpoints with Pre-specified Hypothesis Tests

- Angiographic in-segment late loss (LL) at 13 months
- IVUS-assessed in-device mean lumen area change from post-procedure to 3 years follow-up
- Angiographic in-device mean lumen diameter change between pre- and post-nitrate infusion at 3 years follow-up

Other Endpoints: Cardiac events including all death, cardiac death, MI, and repeat revascularization.

Design: A prospective, randomized, active-controlled, single-blinded, multicenter trial.

Randomization: Subjects were randomly assigned to the BVS or XIENCE group in a 2:1 ratio, stratified by diabetes mellitus and number of lesions to be treated (single target lesion vs. two target lesion vs. one target lesion and one non-target lesion).

Key Inclusion Criteria (Similar to ABSORB III)

- Evidence of myocardial ischemia (*e.g.*, stable or unstable angina, silent ischemia
- One (target) or two (two target lesions or one target and one non-target) *de novo* lesions each in a different native epicardial coronary artery
- RVD (D_{max}) assessed by visual estimation ≥2.5 mm and ≤3.75 mm (vessel sizing using IVUS, OCT or on-line QCA optional)
- Lesion length by visual estimation ≤24 mm
- Visually estimated diameter stenosis ≥50% and <100% with TIMI flow of >1

Key Exclusion Criteria (Similar to ABSORB III)

- AMI within 72 hours of the index procedure
- LVEF <30%
- Subject receiving chronic anticoagulation therapy
- Subject with known renal insufficiency as based on documented diagnosis in medical records, an estimated GFR <30 ml/min/1.73m^2, or dialysis at the time of screening
- Subject requires at least two lesion treatment and is more suitable for staged PCI
- Lesion prevents complete balloon pre-dilatation or heavily calcified
- Anatomy proximal to or within the lesion that prevents placement of delivery system
- Extreme angulation (≥90°) proximal to or within the target lesion
- Excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion

- Lesion located within or distal to a diseased arterial graft or SVG
- Aorto-ostial lesion (within 3 mm of the aorta junction)
- Lesion located in the left main
- Lesion located within 3 mm of the origin of the LAD or LCX
- Lesion involving a bifurcation with a side branch:
    - ≥2 mm in diameter and/or ostial lesion ≥50% stenosis;
    - Requiring protection guide wire; or
    - Requiring pre-dilatation
- Target vessel contains thrombus

PCI Treatment

- Mandatory target lesion pre-dilatation
- Recommended that a minimum of 2 mm of non-diseased tissue be covered by the study device on either side of the lesion.
- Planned overlapping treatment of the target lesion not allowed.
- If a subject has only one target lesion eligible to be treated with the study device, the additional non-target lesion (if present) can be treated with XIENCE.
- The non-target lesions must be treated first, prior to randomization, and the subject can only be randomized if treatment of the non-target lesion was successful and uncomplicated.

Antiplatelet Therapy

- Pre-procedure
    - Loading dose of aspirin and an ADP antagonist (clopidogrel or ticlopidine) per site standard dose and schedule. A loading dose may be omitted for those subjects on chronic therapy for ≥4 days.
- Post-procedure
    - All subjects must be maintained on an IFU-specified dose of ADP antagonist for a minimum of 12 months, and aspirin (80 mg) for an indefinite period after the index procedure.

Study sites and dates of enrollment: Between April 27th, 2013 and December 27th, 2013, 400 subjects from 38 Japanese investigational sites were registered and randomly assigned to the BVS group (266 subjects) or the XIENCE group (134 subjects). Subjects were allocated to one of three imaging subgroups: IVUS (149 subjects), OCT 1 (126 subjects), or OCT 2 (125 subjects) based on method and schedule of intravascular imaging.

Follow up schedule:

- Clinical follow-up at 30 days, 180 days, and at 1, 2, 3, 4 and 5 years.
- All subjects undergo coronary angiography pre- and post-procedure, at 13 months and at 3 years. IVUS subgroup to undergo IVUS post-index procedure and at 3 years.
- OCT 1 subgroup to undergo OCT post-index procedure and at 2 and 3 years.
- OCT 2 subgroup to undergo OCT only at 3 years (no post-procedure OCT).
- Multi-slice CT scan at 13 months and 3 years (150 subjects),
- Acetylcholine vasoreactivity test at 4 years in (120 subjects).

Statistical Analyses:

- The primary analysis population is the ITT cohort.
- The 1-year TLF primary endpoint will be tested for non-inferiority of the BVS vs. XIENCE with a non-inferiority margin of 8.6% at one-sided alpha level of 0.05.
- The powered secondary endpoint of in-segment late loss LL at 13 months will be tested for non-inferiority with a non-inferiority margin of 0.195 mm using one-sided alpha of 0.05.
- For the powered secondary endpoints of vasomotor function and change of mean lumen area, subjects from the Imaging Cohort of ABSORB III trial will be pooled with ABSORB Japan subjects for superiority testing.
- For powered secondary endpoints analysis, lesions from the Full Analysis Set population, defined as subjects who have received only study device at the target lesion, are included.

Results

- **Study Population Demographics:** The mean age was 67.1 ± 9.4 years in the BVS group and 67.3 ± 9.6 years in the XIENCE group and subjects were predominantly male (78.9% in the BVS group, 73.9% in the XIENCE group). There was a high prevalence of hypertension (78.2% vs 79.9%) and dyslipidemia (82.0% vs 82.1%) in the BVS and XIENCE groups, respectively. Diabetes was present in 36.1% and 35.8% of BVS and XIENCE subjects, respectively). The proportion of patients with two (or more) lesions treated were 10.9% (29/266) in the BVS group and 9.7% (13/134) in the XIENCE group.
- **Accountability of Subjects:** A total of 275 lesions were treated in 266 BVS subjects and 137 lesions in 134 XIENCE subjects. Early termination at 1 year, due to consent withdrawal or death, affected 4 subjects in the BVS group and 1 subject in the XIENCE group. Two subjects (1 in the BVS group and 1 in the XIENCE group) who withdrew consent but had no known cardiac events (death, MI, or revascularization) were excluded from the analysis. All subjects have completed 1-year clinical follow-up and follow-up through 5 years is ongoing.

Safety and Effectiveness: The 1-year safety and effectiveness results for ABSORB Japan are presented in Table A6-1.

Table A6-1. ABSORB Japan Clinical Results (ITT Population) – 1 Year Results

	BVS (N = 266)	XIENCE (N = 134)	Difference [95% CI][1]
TLF	4.2% (11/265)	3.8% (5/133)	0.39% [-4.68%, 4.18%]
EFFECTIVENESS			
Ischemia-Driven TLR	2.6% (7/265)	2.3% (3/133)	0.39% [-4.00%, 3.48%]
Ischemia-Driven TVR	4.9% (13/265)	3.8% (5/133)	1.15% [-4.00%, 5.09%]
SAFETY			
All Death	0.8% (2/265)	0.0% (0/133)	0.75% [-2.11%, 2.71%]
Cardiac Death	0.0% (0/265)	0.0% (0/133)	0.00% [-2.81%, 1.43%]
Vascular Death	0.4% (1/265)	0.0% (0/133)	0.38% [-2.45%, 2.11%]
Non-cardiovascular Death	0.4% (1/265)	0.0% (0/133)	0.38% [-2.45%, 2.11%]
TV-MI	3.4% (9/265)	2.3% (3/133)	1.14% [-3.32%, 4.43%]
QMI	1.1% (3/265)	0.0% (0/133)	1.13% [-1.77%, 3.27%]
NQMI	2.3% (6/265)	2.3% (3/133)	0.01% [-4.33%, 2.99%]
All MI	3.4% (9/265)	2.3% (3/133)	1.14% [-3.32%, 4.43%]
QMI	1.1% (3/265)	0.0% (0/133)	1.13% [-1.77%, 3.27%]
NQMI	2.3% (6/265)	2.3% (3/133)	0.01% [-4.33%, 2.99%]
Cardiac Death or MI	3.4% (9/265)	2.3% (3/133)	1.14% [-3.32%, 4.43%]
ARC-defined Definite + Probable Scaffold/Stent Thrombosis (0-365 days)	1.5% (4/262)	1.5% (2/133)	0.02% [-3.90%, 2.60%]
Acute (≤ 1 day)	0.0% (0/266)	0.0% (0/133)	0.00% [-2.81%, 1.42%]
Sub-Acute (> 1-30 days)	1.1% (3/265)	0.8% (1/133)	0.38% [-3.09%, 2.61%]
Late (31-365 days)	0.4% (1/262)	0.8% (1/133)	-0.37% [-3.77%, 1.48%]

[1] Without multiplicity adjustment.
Note: 1-year timeframe includes a window of ± 28 days.
Note: MI is per protocol definition (Same as per protocol ABSORB III definition)

The 13 month angiographic endpoint results (in-segment late loss) were recently published in the European Heart Journal, but these data were not provided by the sponsor for FDA review.

Summary of Study Results

- The 1-year TLF primary endpoint rate was 4.2% (11/265) in BVS group and 3.8% (5/133) in the XIENCE group. The non-inferiority endpoint for the BVS vs. XIENCE was met (p <0.0001); however, the non-inferiority margin (8.6%) was large.
- There were no cardiac deaths
- The target vessel MI rates were 3.4% (9/265) and 2.3% (3/133) in the BVS and XIENCE groups, respectively.
- The ID-TLR rates were 2.6% (7/265) and 2.3% (3/133) in the BVS and XIENCE groups, respectively.
- The 1-year ARC definite plus probable scaffold/stent thrombosis rates were 1.5% in both groups.

Appendix 7

Treatment of Target Vessels with a Core Lab-Assessed RVD ≥2.25 mm Vs. <2.25 mm in Non-US BVS Studies: ABSORB Cohort B, ABSORB EXTEND, ABSORB II and ABSORB JAPAN

Table A7-1 shows 1-year clinical outcomes for the ABSORB Cohort B and ABSORB EXTEND studies, and Table A7-2 shows 1-year clinical outcomes for the ABSORB II and ABSORB JAPAN trials. BVS implantation in vessels with an RVD <2.25 mm was associated with generally higher event rates vs. vessels with an RVD ≥2.25 mm. These results are consistent with the trends seen in the pivotal ABSORB III trial. In reviewing the data in Table A7-1, the following caveats that limit the conclusions that can be drawn from these studies should be considered: (1) Smaller sample sizes in the individual non-US studies compared with ABSORB III; (2) missing data; (3) different enrollment criteria among studies; and (4) different MI definitions among studies.

It should be noted that quantitative imaging assessment techniques (including on-line QCA or IVUS) were utilized per protocol in the ABSORB Extend and ABSORB II studies.

Table A7-1. ABSORB Cohort B and ABSORB EXTEND: Subgroup Information and 1-Year Clinical Outcomes Stratified by Core Laboratory-Assessed RVD – Per-Subject Analysis (ITT Population)

ABSORB Cohort B[1,2]	Overall ITT Population BVS (N=101)	RVD ≥2.25 mm BVS (N=80)	RVD <2.25 mm BVS (N=17)
TLF	6.9% (7/101)	5.0% (4/80)	11.8% (2/17)
Cardiac Death	0.0% (0/101)	0.0% (0/80)	0.0% (0/17)
TV- MI	3.0% (3/101)	1.3% (1/80)	5.9% (1/17)
ID-TLR	4.0% (4/101)	3.8% (3/80)	5.9% (1/17)
Scaffold/Stent/ Thrombosis (Def/Prob)	0.0% (0/101)	0.0% (0/80)	0.0% (0/17)
ABSORB EXTEND[3,4]	**Overall ITT Population BVS (N=812)**	**RVD ≥2.25 mm BVS (N=675)**	**RVD <2.25 mm BVS (N=124)**
TLF	5.0% (41/812)	4.7% (32/675)	5.6% (7/124)
Cardiac Death	0.7% (6/812)	0.6% (4/675)	0.0% (0/124)
TV- MI	3.0% (24/812)	2.8% (19/675)	3.2% (4/124)
ID-TLR	2.3% (19/812)	2.1% (14/675)	2.4% (3/124)
Stent/Scaffold Thrombosis (Def/Prob)	0.99% (8/809)	0.89% (6/672)	0.0% (0/124)

[1]ABSORB Cohort B: Four patients had missing QCA RVD, also missing visual RVD with no other imaging measurements available
[2]ABSORB Cohort B MI definition: WHO definition (see Appendix 10)
[3]ABSORB EXTEND: 13 subjects had missing QCA RVD data. There were a total of 8 device thrombosis at 1 year, and 2 of these patients with device thrombosis had missing QCA RVD data.
[4]ABSORB EXTEND MI definition: Per ABSORB-III protocol MI definition (see Appendix 9)

Table A7-2. ABSORB II and ABSORB JAPAN: Subgroup Information and 1-Year Clinical Outcomes Stratified by Core Laboratory Assessed RVD – Per-Subject Analysis (ITT Population)

ABSORB II[1]	Overall ITT Population		RVD ≥2.25 mm		RVD <2.25 mm	
	BVS (N=335)	XIENCE (N=166)	BVS (N=259)	XIENCE (N=133)	BVS (N=72)	XIENCE (N=30)
TLF	6.0% (20/331)	4.2% (7/165)	5.0% (13/259)	4.5% (6/133)	9.7% (7/72)	3.3% (1/30)
Cardiac Death	0.0% (0/331)	0.0% (0/165)	0.0% (0/259)	0.0% (0/133)	0.0% (0/72)	0.0% (0/30)
TV- MI	5.4% (18/331)	2.4% (4/165)	4.6% (12/259)	3.0% (4/133)	8.3% (6/72)	0.0% (0/30)
ID-TLR	1.2% (4/331)	1.8% (3/165)	0.8% (2/259)	1.5% (2/133)	2.8% (2/72)	3.3% (1/30)
Stent/Scaffold Thrombosis (Def/Prob)	0.9% (3/329)	0.0% (0/164)	0.8% (2/257)	0.0% (0/132)	1.4% (1/72)	0.0% (0/30)
ABSORB JAPAN[1]	**Overall ITT Population**		**RVD ≥2.25 mm**		**RVD <2.25 mm**	
	BVS (N=266)	**XIENCE (N=134)**	**BVS (N=224)**	**XIENCE (N=117)**	**BVS (N=41)**	**XIENCE (N=17)**
TLF	4.2% (11/265)	3.8% (5/133)	4.5% (10/223)	1.7% (2/116)	2.4% (1/41)	17.6% (3/17)
Cardiac Death	0.0% (0/265)	0.0% (0/133)	0.0% (0/223)	0.0% (0/116)	0.0% (0/41)	0.0% (0/17)
TV- MI	3.4% (9/265)	2.3% (3/133)	3.6% (8/223)	1.7% (2/116)	2.4% (1/41)	5.9% (1/17)
ID-TLR	2.6% (7/265)	2.3% (3/133)	2.7% (6/223)	0.0% (0/116)	2.4% (1/41)	17.6% (3/17)
Stent/Scaffold/Stent Thrombosis (Def/Prob)	1.5% (4/262)	1.5% (2/133)	1.4% (3/220)	0.9% (1/116)	2.4% (1/41)	5.9% (1/17)

[1]ABSORB II and ABSORB JAPAN MI definitions: Per ABSORB-III protocol MI definition (see Appendix 9)

Appendix 8

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

General inclusion criteria

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

General exclusion criteria

- #1 Any surgery requiring general anesthesia or discontinuation of aspirin and/or an ADP antagonist is planned within 12 months after the procedure.
- #3 Subject has known allergic reaction, hypersensitivity or contraindication to aspirin; or to clopidogrel and prasugrel and ticagrelor; or to heparin and bivalirudin, and therefore cannot be adequately treated with study medications.
- #4 Subject had an acute MI (AMI, STEMI or NSTEMI) within 72 hours of the index procedure and both CK and CK-MB have not returned to within normal limits at the time of index procedure; or subject with stable angina or silent ischemia has CK-MB that is greater than normal limits at the time of the index procedure.
- #5 Subject is currently experiencing clinical symptoms consistent with new onset AMI (STEMI or NSTEMI), such as nitrate-unresponsive prolonged chest pain with ischemic ECG changes.
- #7 Subject has a left ventricular ejection fraction <30% assessed by any quantitative method, requires future staged PCI either in target or non-target vessels.
- #8 Subject has undergone prior PCI within the target vessel during the last 12 months. Prior PCI within the non-target vessel or any peripheral intervention is acceptable if performed anytime >30 days before the index procedure, or between 24 hours and 30 days before the index procedure if successful and uncomplicated.
- #9 Subject requires future staged PCI either in target or non-target vessels or subject requires future peripheral interventions <30 days after the index procedure.
- #17 Subject has renal insufficiency as defined as an estimated GFR <30 ml/min/1.73m2 or dialysis at the time of screening.

All angiographic inclusion and exclusion criteria

Select treatment strategies:

- Non-target lesion treatment not per protocol
- Target lesion treated not per protocol
- Pre-dilatation not done per protocol
- ≥1 target lesion(s) in which different devices were used in each lesion – semi-crossover.

- Treatment of >2 lesions or two lesions in the same vessel
    - Subject enrolled after unsuccessful treatment of non-target lesion

Appendix 9: Definitions

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

ANGINA PECTORIS

Braunwald Classification of Unstable Angina

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

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

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

Canadian Cardiovascular Society (CCS) Classification of Stable Angina

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

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

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

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

ANGIOGRAPHIC BINARY RESTENOSIS (ABR): Re-narrowing of the artery with a percent diameter stenosis ≥50%.

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

Type A Lesions (High Success, >85%; Low Risk)
• 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)
• 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: ≥ two adverse characteristics

Type C Lesions (Low Success, <60%; High Risk)

- Total occlusions > 3 mo old
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

AS-TREATED POPULATION: The as-treated population consists of subjects who have received only study device(s) (BVS or XIENCE) at the target lesion. Subjects were included in the treatment group corresponding to the study device actually received. Subjects with ≥1 target lesion(s) in which different devices were used in each lesion were excluded**.**

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

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

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

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

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

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

DEATH (Per ARC Circulation 2007; 115: 2344-2351)**:** All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (*e.g.*, cancer, infection) should be classified as cardiac.

Cardiac death: Any death due to proximate cardiac cause (*e.g.*, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment.
Vascular death: Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
Non-cardiovascular death: Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

DEVICE DEFICIENCY (ISO14155 3.15)**:** Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance ISO14155 3.15. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

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

ENROLLED SUBJECT: Subject has signed the Informed Consent.

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

IN-SCAFFOLD: Within the margins of the scaffold.

IN-SEGMENT: Within the margins of the stent or scaffold and 5 mm proximal and 5 mm distal to the stent or scaffold.

IN-STENT: Within the margins of the stent.

INTENT-TO-TREAT (ITT) POPULATION: The intent-to-treat (ITT) population is defined as the subjects registered in the study at the point of randomization, regardless of the treatment actually received. Subjects are analyzed in the treatment group to which they were randomized.

LATE LOSS (LL): General definition: Calculated as MLD post-procedure – MLD at follow-up

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

MAJOR EPICARDIAL VESSELS:

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

MYOCARDIAL INFARCTION (MI)

Myocardial Infarction (Protocol MI Definition)

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

Classification	Biomarker Criteria	Additional Criteria
ULN=Upper limits of the local laboratory normal (will be collected from each hospital laboratory prior to study commencement); LBBB=Left Bundle-branch Block * Baseline CKMB value is required before study procedure and presumes a typical rise and fall post procedure to diagnose a peri procedure MI ** Whenever at least one baseline and one post procedure CK-MB measure are available, adjudication of MI will be based solely on these biomarker values. If the patient has stable ischemic heart disease and the baseline CK-MB measure are not available, they will be assumed to be within normal limits and MI will be adjudicated by the CEC solely according to the post procedure CK-MB measures. TROPONINS WILL NOT BE USED TO DIAGNOSE PERI-PROCEDURAL MI. If the patient had an elevated CK-MB at baseline (protocol violation), and/or no post procedure CKMB measures are available (protocol violation), adjudication of a post procedure MI will be based on presence of two of the following three: 1) New ST elevation or ST depression ≥0.1mV in ≥2 contiguous leads on ECG ≥30 min. and ≤48 hrs. post-PCI (Note: ST elevation should be measured at the J point, and ST depression must be horizontal or down-sloping), Or New pathological Q-waves in ≥2 contiguous leads, or new LBBB; 2) Post procedure TIMI 0/1 flow in a coronary artery or a side branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline (core laboratory assessed); 3) Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality. Note: Patients with stable coronary artery disease syndromes may have the baseline CKMB drawn from the arterial sheath during the PCI procedure. If this value is elevated (expected in 1-2% of patients with stable CAD, a post-PCI MI will be diagnosed if the post-procedure CK-MB shows a 20% or greater CK-MB increase on the second sample drawn 3 to 12 hours post procedure (meeting the threshold of CKMB > 5 x ULN), and at least 1 of the following are present: 1) ECG changes indicative of new ischemia - (new ST-T changes or new LBBB), 2) Development of pathological Q waves; 3) Imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality. In the absence of any of the above evidence, a >50% increase in CK-MB over the baseline value, meeting the threshold of CKMB >5 x ULN, will also qualify for a peri-procedural MI.		

Peri-procedural MI After PCI: The peri-procedural period includes the first 48 hours after PCI.

Peri-procedural MI After CABG: The peri-procedural period includes the first 48 hours after coronary artery bypass grafting

Spontaneous MI: MI after the peri-procedural 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 peri-procedural MI of any elevation of troponin or CKMB above the 99th percentile of the upper range limit (or ULN if URL is not available) is used. All late events that are not associated with a revascularization procedure will be considered simply as spontaneous.

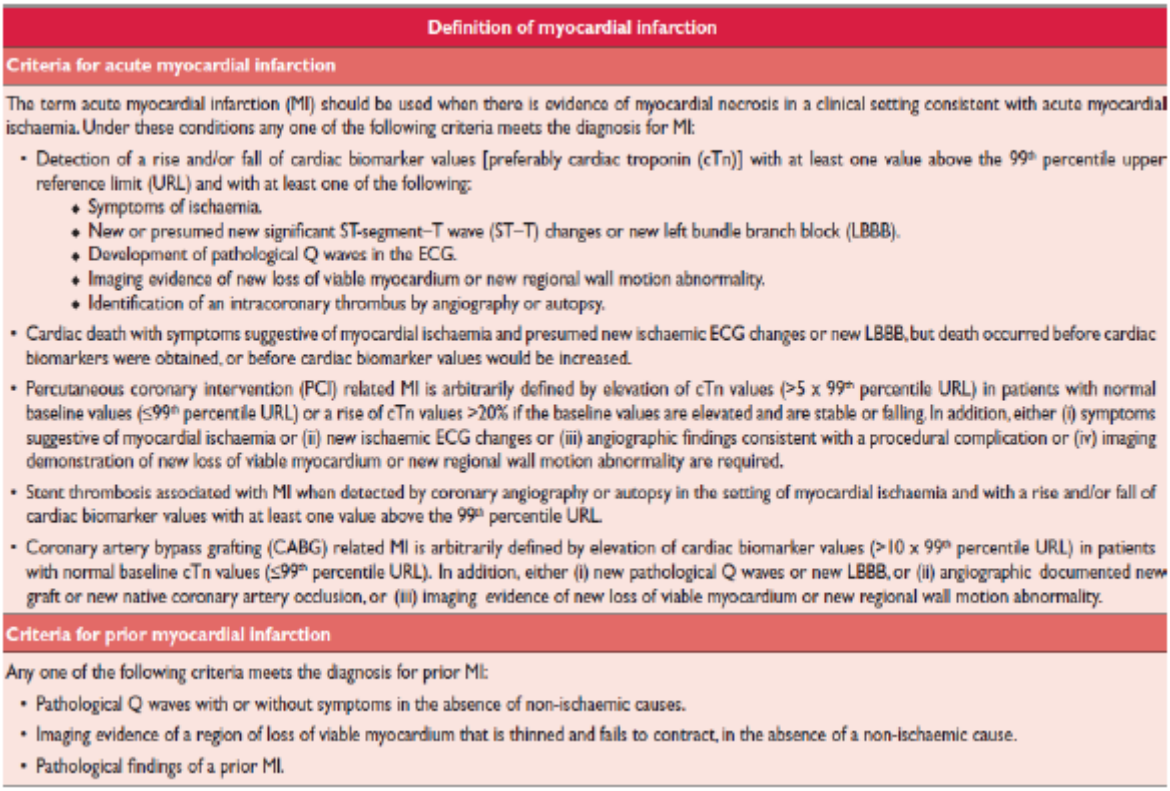
Myocardial infarctions will also be adjudicated based on the following classification:

Q-wave MI: Development of new, pathological Q wave on the ECG ($\geq$ 0.04 seconds in duration and $\geq$ 1 mm in depth) in $\geq$ 2 contiguous precordial leads or $\geq$ 2 adjacent limb leads)

Non-Q wave MI: Those MIs that are not Q-wave MI.

Myocardial infarctions will also be adjudicated as to their relation to the Target Vessel. All infarcts that cannot be clearly attributed to a vessel other than the target vessel will be considered related to the target vessel.

Universal Myocardial Infarction Definition: As a secondary analysis, MIs were adjudicated according to the 2012 Universal Definition (Thygesen K et al. Eur Heart J. August 24, 2012)



Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

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

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

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

Q-wave MI: Development of new, pathological Q wave on the ECG

Non-Q wave MI: Elevation of CK levels to ≥2 times the upper limit of normal (ULN) with elevated CK-MB in the absence of new pathological Q waves. Non-Q wave MI definition were used for both peri-procedural MI definition (≤48 hours post-procedure) and spontaneous (>48 hours post-procedure).

PERCUTANEOUS CORONARY INTERVENTION (PCI): Refers to all interventional cardiology methods for treatment of coronary artery disease.

PER-TREATMENT-EVALUABLE (PTE) POPULATION: The per-treatment evaluable (PTE) population consists of subjects who have received only study device(s) (BVS or XIENCE) at the target lesion. The PTE population is analyzed on the treatment actually received, and excludes subjects with protocol deviations that are described in Appendix 9.

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

- For randomized subjects: RVD remains ≥2.50 mm - ≤3.75 mm and lesion length that will be covered by the device (including any edge dissections) is still ≤24 mm
  - For Lead-In subjects: RVD remains ≥2.75 mm - ≤3.25 mm and length of the lesion that will be covered by the device (including any edge dissections) is still ≥8 mm - ≤14 mm
- Residual %DS is a maximum of <40% (per visual estimation), ≤20% is strongly recommended.
- TIMI Grade-3 flow (per visual estimation),

- No angiographic complications (*e.g.*, distal embolization, side branch closure),
- No dissections NHLBI grade D-F
- No chest pain lasting > 5 minutes
- No ST depression or elevation lasting > 5 minutes.

RANDOMIZED SUBJECT: Subject is considered randomized after the IVRS has been called and a device (BVS or XIENCE) has been assigned.

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

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

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

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

Non Target Lesion Revascularization (Non-TLR): Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

Non Target Vessel Revascularization (Non-TVR): Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Non-Treated Vessel: Vessel not treated at the time of the index procedure.

Non-Treated Vessel Revascularization: Revascularization of the non-treated vessel.

Ischemia Driven (ID) Revascularization (ID-TLR/ID-TVR): A revascularization is considered ischemia-driven if associated with any of the following:

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

STENT THROMBOSIS (Per ARC Circulation 2007; 115: 2344-2351)**:** Stent Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject left the catheterization lab.

Timing

- Acute stent thrombosis:* 0 - 24 hours post stent implantation
- Subacute stent thrombosis:* >24 hours to 30 days post stent implantation
- Late stent thrombosis:† 30 days - 1 year post stent implantation

- Very late stent thrombosis:† >1 year post stent implantation
  *Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0-30 days) – this definition is currently used in the community.
  †Including "primary" as well as "secondary" late stent thrombosis; "Secondary" late stent thrombosis is a stent thrombosis after a target segment revascularization.

Categories (Definite, Possible and Probable):

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

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

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

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

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

Possible stent thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.
For the present study the principal definition of stent thrombosis will be ARC definite or probable stent thrombosis.

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.

Maximum Diameter (D_{max}): D_{max} refers to maximum lumen diameter evaluated after pre-dilatation within the boundaries of intended scaffold segment.

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

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

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

Thrombosis In Myocardial Infarction (TIMI) Flow Grades

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

TARGET LESION (Analysis Definition): The target lesion is defined as the lesion that has met the angiographic inclusion and exclusion criteria in a registered subject upon calling the interactive voice response system (IVRS). Under these conditions, the lesion is considered the target lesion regardless of the device implantation and treatment actually received.

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

REFERENCES

1. Gada H, Kirtane AJ, Newman W, Sanz M, Herrniller JB, Mahaffey KW, Cutlip DE, Sudhir K, Hou L, Koo K., Stone GW. 5-Year Results of a Randomized Comparison of XIENCE V Everolimus-Eluting and TAXUS Paclitaxel-Eluting Stents: Final Results From the SPIRIT III Trial (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With *de Novo* Native Coronary Artery Lesions).

2. Brener SJ, Kereiakes DJ, Simonton CA, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Smith RS Jr, Ying SW, Cutlip DE, Stone GW. Everolimus-eluting stents in patients undergoing percutaneous coronary intervention: final 3-year results of the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With *de Novo* Native Coronary Artery Lesions trial. *Am Heart J.* 20 13; 166: I 035-42.

3. Yamaji K, Kimura T, Morimoto T, Nakagawa Y, Inoue K, Soga Y, Arita T, Shirai S, Ando K, Kondo K, Sakai K, Goya M, lwabuchi M, Yokoi H, Nosaka H, Nobuyoshi M. Very long-term (15 to 20 years) clinical and angiographic outcome after coronary bare metal stent implantation. *Circ Cardiovasc Interv.* 20 I 0;3:468-75.