SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Drug Eluting Coronary System (NIQ)

Product Device Trade Name: Absorb GT1™ Bioresorbable Vascular Scaffold (BVS) System

Applicant's Name and Address: Abbott Vascular
3200 Lakeside Drive
Santa Clara, CA 95054

Date of Panel Recommendation: March 15, 2016

Premarket Approval Application

(PMA) Supplement Number: P150023

Date of FDA Notice of Approval: TBD

Expedited: Not Applicable

II. INDICATIONS 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.

III. CONTRAINDICATIONS

The Absorb GT1 BVS System is contraindicated for use in:

- Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or post procedural antiplatelet regimen.
- Patients with a known allergy or hypersensitivity to everolimus or structurally related compounds, device materials (poly [L-lactide], poly [D,L-lactide], platinum), or contrast medium who cannot be adequately premedicated.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Absorb GT1 BVS System labeling.

V. DEVICE DESCRIPTION

The Absorb GT1 BVS System is composed of the following components:

- A bioresorbable poly(L-lactide) (PLLA) scaffold backbone
- A coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly(D,L-lactide) (PDLLA)
- Four platinum marker beads, two each embedded at the proximal and distal ends of the scaffold for radiopacity
- An optimized delivery system (ODS) that leverages technology advancements of the XIENCE family of products[1], and incorporates design features from the Absorb BVS, XIENCE Xpedition®, and XIENCE Alpine™ delivery systems

The product description for the Absorb GT1 BVS System is detailed below in **Table V-1**. The Absorb GT1 BVS System size matrix incorporates a small and medium scaffold design. The small design is available in 2.5, and 3.0 mm diameters in lengths of 8, 12, 18, 23, and 28 mm. The medium design is available in a 3.5 mm diameter in lengths of 12, 18, 23, and 28 mm. The Absorb GT1 BVS System is available in a Rapid Exchange (RX) configuration.

[1] XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V Stent System; **P070015**, approved July 2, 2008), the XIENCE nano® Everolimus Eluting Stent System (XIENCE nano Stent System; **P070015/S054**, approved May24, 2011), the XIENCE PRIME® and XIENCE PRIME® LL Everolimus Eluting Coronary Stent System (XIENCE PRIME Stent System; **P110019**, approved November 1, 2011), the XIENCE Xpedition®, XIENCE Xpedition® Small Vessel (SV) and XIENCE Xpedition® Long Length (LL) Everolimus Eluting Coronary Stent System (XIENCE Xpedition Stent System; **P110019 / S025**, approved December 21, 2012), and the XIENCE Alpine™ Everolimus Eluting Coronary Stent System (XIENCE Alpine Stent System; **P110019/S070**; approved September 3, 2014).

Table V-1 Absorb GT1 BVS System Product Description

<table>
<tr><td>Available Stent Lengths (mm)</td><td>8, 12, 18, 23, and 28</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td>2.5, 3.0, and 3.5</td></tr>
<tr><td>Stent Material</td><td>Poly(L-lactide)</td></tr>
<tr><td>Drug Component</td><td>
<table>
<tr><th>Scaffold Design</th><th>Scaffold Diameter (mm)</th><th>Scaffold Length (mm)</th><th>Scaffold Surface Area (cm^2)</th><th>Drug Dose Density ($\mu g/cm^2$)</th><th>Target Drug Amount (µg)</th></tr>
<tr><td rowspan="5">Small</td><td rowspan="5">2.5 / 3.0</td><td>8</td><td>0.76</td><td rowspan="9">100</td><td>76</td></tr>
<tr><td>12</td><td>1.14</td><td>114</td></tr>
<tr><td>18</td><td>1.81</td><td>181</td></tr>
<tr><td>23</td><td>2.28</td><td>228</td></tr>
<tr><td>28</td><td>2.76</td><td>276</td></tr>
<tr><td rowspan="4">Medium</td><td rowspan="4">3.5</td><td>12</td><td>1.35</td><td>135</td></tr>
<tr><td>18</td><td>1.97</td><td>197</td></tr>
<tr><td>23</td><td>2.46</td><td>246</td></tr>
<tr><td>28</td><td>3.08</td><td>308</td></tr>
</table>
</td></tr>
<tr><td>Delivery System Working Length</td><td>143 cm</td></tr>
<tr><td>Delivery System</td><td>Single access port to inflation lumen; guide wire exit notch is located 26 cm from tip; designed for guide wires ≤ 0.014”.</td></tr>
<tr><td>Scaffold Delivery System Balloon</td><td>A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded scaffold length</td></tr>
<tr><td>Balloon Inflation Pressure</td><td>Rated Burst Pressure (RBP): 16 atm (235 psi)
<table>
<tr><th>Stent Diameter (mm)</th><th>In vitro Stent Nominal Pressure (atm)</th></tr>
<tr><td>2.5</td><td>6</td></tr>
<tr><td>3.0</td><td>7</td></tr>
<tr><td>3.5</td><td>6</td></tr>
</table>
</td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td>≥ 6 F (0.066”)</td></tr>
<tr><td>Catheter Shaft Outer Diameter</td><td>Distal: 0.039” ± 0.002” (0.99 mm ± 0.05 mm)
Proximal: ≤ 0.029” (0.74 mm)</td></tr>
</table>

A. Device Component Description

The Absorb GT1 BVS System consists of a polymeric scaffold mounted on an optimized delivery system (ODS). The scaffold is manufactured from the bioresorbable polymer poly(L-lactide) (PLLA), a semicrystalline polymer whose degree of crystallinity and crystalline microstructure are dictated by the thermal and deformation history during processing. The high tensile strength and modulus of PLLA make it suitable for load bearing

applications. Two platinum markers are embedded at each end ring to enable fluoroscopic visualization.

The optimized delivery system (ODS) incorporates design features from the Absorb BVS, XIENCE Xpedition, and XIENCE Alpine delivery systems. The ODS is a rapid-exchange (RX) design with the balloon and scaffold at the distal end of the catheter. For the RX design, the proximal lumen provides for inflation of the balloon with contrast medium and the central distal lumen permits a guidewire to facilitate advancement of the catheter. The distal catheter shaft, the tip, and tapers of the balloon are coated with HYDROCOAT™ Hydrophilic Coating.

Radiopaque markers are positioned underneath the balloon to provide accurate positioning of the scaffold / balloon in the artery. The balloon is designed to deliver an expandable scaffold of known diameter and length at specified pressures. Markers located on the proximal outer shafts 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 is designed with a luer-lock fitting to facilitate connection to an inflation device.

B. Drug Component Description

The Absorb GT1 BVS is coated with a drug / polymer matrix that consists of 50 wt% PDLLA and 50 wt% of the active pharmaceutical ingredient, everolimus, the same drug utilized for the XIENCE family of products. Neither a primer coat nor a topcoat layer is utilized for the Absorb GT1 BVS. The Absorb GT1 BVS also utilizes the same drug dose density (100 $\mu g/cm^2$) and similar coating technologies as XIENCE family of products.

B1. Everolimus

Everolimus (Chemical name: 40-O-(2-hydroxyethyl)-rapamycin) (**Figure V-1**) is a novel semisynthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: Sirolimus) is a secondary macrolide metabolite that is produced by certain actinomycete strains.

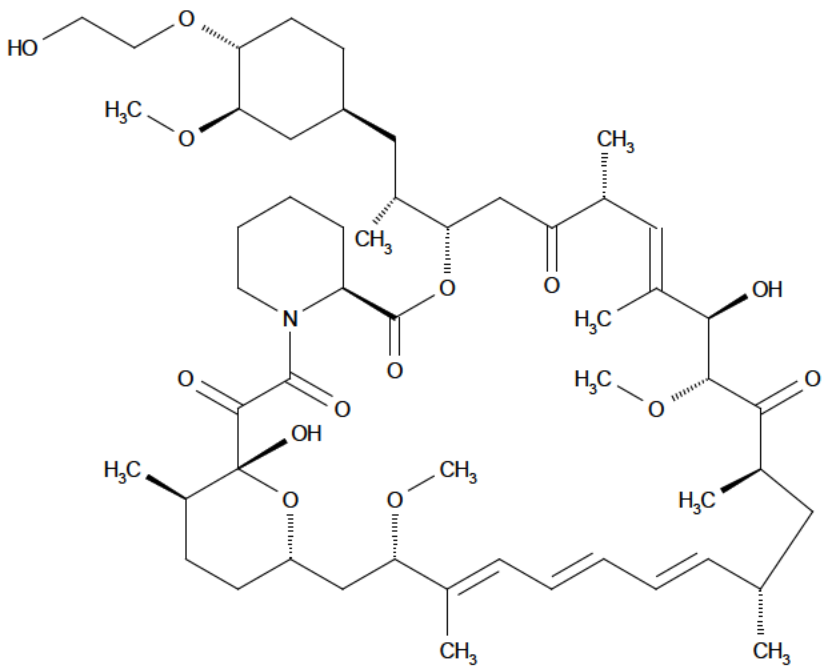


Figure V-1 Chemical Structure of Everolimus

B2. Inactive Ingredients

The Absorb GT1 BVS System contains poly(D,L-lactide) (PDLLA), random copolymer with equimolar subunits of D- and L-lactic acid. PDLLA is used to contain and control the release of everolimus. PDLLA is characterized by a lower tensile strength and higher elongation than poly(L-lactide) (PLLA) due to its amorphous nature.

C. Mechanism of Action

The mechanism by which the Absorb GT1 BVS inhibits neointimal growth as seen in preclinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP- 12 Rapamnycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, coated stents, and drug-eluting stents), and coronary artery bypass grafting (CABG) surgery. Each alternative has its own advantages

and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Absorb GT1 BVS System is commercially available in the following countries:

- AFGHANISTAN
- ALBANIA
- ARUBA
- AUSTRIA
- AZERBAIJAN
- BAHAMAS
- BAHRAIN
- BANGLADESH
- BARBADOS
- BELGIUM
- BRUNEI
- BULGARIA
- CAMBODIA
- CHILE
- CYPRUS
- CZECH REPUBLIC
- DENMARK
- DOMINICAN REP.
- ESTONIA
- FINLAND
- FRANCE
- FREN.POLYNESIA
- FRENCH GUYANA
- GEORGIA
- GERMANY
- GREECE
- GUADELOUPE
- HONG KONG
- HUNGARY
- ICELAND
- IRAQ
- IRELAND
- ITALY
- JAMAICA
- JORDAN
- KOSOVO
- KUWAIT
- LATVIA
- LEBANON
- LIBYA
- LIECHTENSTEIN
- LITHUANIA
- LUXEMBOURG
- MALAYSIA
- MALTA
- MARTINIQUE
- MAURITIUS
- MOROCCO
- NEPAL
- NETHERLANDS
- NEW CALEDONIA
- NEW ZEALAND
- NORWAY
- OMAN
- PANAMA
- PARAGUAY
- POLAND
- PORTUGAL
- QATAR
- REP. OF ARMENIA
- REP. OF YEMEN
- REUNION
- ROMANIA
- SAUDI ARABIA
- SLOVAKIA
- SLOVENIA
- SPAIN
- SWEDEN
- SWITZERLAND
- THAILAND
- TRINIDAD,TOBAGO
- TUNISIA
- TURKEY
- UNIT.ARAB EMIR.
- UNITED KINGDON

The Absorb BVS System is commercially available in the following countries:

- AFGHANISTAN
- ALBANIA
- ARGENTINA
- ARUBA
- AUSTRALIA
- AUSTRIA
- AZERBAIJAN
- BAHAMAS
- BAHRAIN
- BANGLADESH
- BARBADOS
- BELARUS
- BELGIUM
- BRAZIL
- BRUNEI
- BULGARIA
- CAMBODIA
- CHILE
- COLOMBIA
- COSTA RICA
- CYPRUS
- CZECH REPUBLIC
- DENMARK
- DOMINICAN REP.
- EQUADOR
- EGYPT
- ESTONIA
- FINLAND
- FRANCE
- FREN.POLYNESIA

- FRENCH GUYANA
- GEORGIA
- GERMANY
- GREECE
- GUADELOUPE
- HONG KONG
- HUNGARY
- ICELAND
- INDIA
- INDONESIA
- IRAN
- IRAQ
- IRELAND
- ISRAEL
- ITALY
- JAMAICA
- JORDAN
- KAZAKHSTAN
- KOSOVO
- KUWAIT
- LATVIA
- LEBANON
- LIBYA
- LIECHTENSTEIN
- LITHUANIA
- LUXEMBOURG
- MACEDONIA
- MALAYSIA
- MALTA
- MARTINIQUE
- MAURITIUS
- MEXICO
- MOROCCO
- NEPAL
- NETHERLANDS
- NEW CALEDONIA
- NEW ZEALAND
- NORWAY
- OMAN
- PAKISTAN
- PANAMA
- PARAGUAY
- PHILIPPINES
- POLAND
- PORTUGAL
- QATAR
- REP. OF ARMENIA
- REP. OF YEMEN
- REUNION
- ROMANIA
- RUSSIAN FED.
- SAUDI ARABIA
- SERBIA
- SINGAPORE
- SLOVAKIA
- SLOVENIA
- SOUTH KOREA
- SPAIN
- SWEDEN
- SWITZERLAND
- TAIWAN
- THAILAND
- TRINIDAD,TOBAGO
- TUNISIA
- TURKEY
- UKRAINE
- UNIT.ARAB EMIR.
- UNITED KINGDOM
- URUGUAY
- UZBEKISTAN
- VENEZUELA
- VIETNAM

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with PCI, treatment procedures and the use of a coronary scaffold in native coronary arteries include the following, but are not limited to:

- Allergic reaction or hypersensitivity to latex, contrast agent, anesthesia, device materials (platinum, or polymer [poly (L-lactide) (PLLA), polymer poly (D,L-lactide) (PDLLA)]), and drug reactions to everolimus, anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
    - Catheter site reactions
    - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Embolism (air, tissue, plaque, thrombotic material or device)
- Coronary artery complications which may require additional intervention, including:
    - Total occlusion or abrupt closure

    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Tissue prolapse / plaque shift
    - Embolism (air, tissue, plaque, thrombotic material or device)
    - Coronary or scaffold thrombosis (acute, subacute, late, very late)
    - Stenosis or restenosis
- Pericardial complications which may require additional intervention, including:
    - Cardiac tamponade
    - Pericardial effusion
    - Pericarditis
- Cardiac arrhythmias (including conduction disorders, atrial and ventricular arrhythmias)
- Cardiac ischemic conditions (including myocardial ischemia, myocardial infarction [including acute], coronary artery spasm and unstable or stable angina pectoris)
- Stroke / Cerebrovascular accident (CVA) and Transient Ischemic Attack (TIA)
- System organ failures:
    - Cardio-respiratory arrest
    - Cardiac failure
    - Cardiopulmonary failure (including pulmonary edema)
    - Renal insufficiency / failure
    - Shock
- Blood cell disorders (including Heparin Induced Thrombocytopenia [HIT])
- Hypotension / hypertension
- Peripheral nerve injury
- Peripheral ischemia
- Infection
- Nausea and vomiting
- Palpitations, dizziness, and syncope
- Chest pain
- Fever
- Pain
- Death

Adverse events associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily can be found in the Summary of Product Characteristics (SPC) and labels for the drug. [2] The risks described below include the anticipated adverse events relevant for the cardiac population referenced in the contraindications, warnings and precaution sections of the everolimus labels / SPCs and / or observed at incidences ≥ 10% in clinical trials with oral everolimus for different indications. Please refer to the drug SPCs and labels for more detailed information and less frequent adverse events.

- Abdominal pain
- Anemia

[2] Certican® UK label Mar 2015, Afinitor® EU authorization SPC Dec 2014, Votubia® EU SPC Sept 2014, Afinitor® US label Jan 2105, and Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

- Angioedema (increased risk with concomitant ACE inhibitor use)
- Arterial thrombotic events
- Bleeding and coagulopathy (including Hemolytic Uremic Syndrome [HUS], Thrombotic Thrombocytopenic Purpura [TTP], and thrombotic microangiopathy-increased risk with concomitant cyclosporine use)
- Constipation
- Cough
- Diabetes mellitus
- Diarrhea
- Dyspnea
- Embryo-fetal toxicity
- Erythema
- Erythroderma
- Headache
- Hepatic Artery Thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, or to other rapamycin derivates
- Hypertension
- Infection (bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Polyoma virus-associated nephropathy (PVAN), JC virus associated progressive multiple leukoencephalopathy (PML), fatal infections and sepsis have been reported in patients treated with oral everolimus.)
- Kidney arterial and venous thrombosis
- Laboratory test alterations (elevations of serum creatinine, proteinuria, hypokalemia; hyperglycemia, dyslipidemia including hypercholesterolemia and hypertriglyceridemia; liver function tests abnormal; decreases in hemoglobin, lymphocytes, neutrophils, and platelets)
- Lymphoma and skin cancer
- Male infertility
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain
- Pancreatitis
- Pericardial effusion
- Peripheral edema
- Pleural effusion
- Pneumonia
- Pyrexia
- Rash
- Renal failure
- Upper respiratory tract infection
- Urinary tract infection

- Venous thromboembolism
- Vomiting
- Wound healing complications (including wound infections and lymphocele)

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A1. Biocompatibility Studies

ISO10993-1 specified biocompatibility tests for blood contact permanent implant (>30 days) were performed for the Absorb GT1 BVS with everolimus (drug scaffold) and without everolimus (polymer only scaffold). These tests include cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity, genotoxicity, implantation, and haemocompatibility. The Absorb GT1 BVS passed all the test criteria (**Table IX-1**).

ISO10993-1 specified biocompatibility tests for externally communicating devices contacting circulating blood (≤ 24 hours) were performed for the optimized delivery system (ODS) for the Absorb GT1 BVS. These tests include cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity (acute), and haemocompatibility. The ODS passed all the test criteria (**Table IX-1**).

All biocompatibility testing was conducted in accordance with one or more of the following regulations and guidance documents:

- ISO 10993 Biological Evaluation of Medical Devices
- Draft Guidance for Industry and Food and Drug Administration Staff – Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"
- Guidance for Industry- Coronary Drug-eluting Stent Nonclinical and Clinical Studies Companion Document
- Good Laboratory Practices Regulations (21 CFR, part 58)

Table IX-1 Biocompatibility Test Summary

Test	Test Description	Test Article and Results
Cytotoxicity	ISO10993-5: MEM Extract or Direct Contact	• Drug scaffold: Pass (non-cytotoxic) • Polymer only scaffold: Pass (non-cytotoxic) • Optimized delivery system: Pass (non-cytotoxic)
Sensitization	ISO10993-10: Maximization Test for Delayed Hypersensitivity	• Drug scaffold: Pass (non-sensitizing) • Polymer only scaffold: Pass (non-sensitizing) • Optimized Delivery System: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO10993-10: Intracutaneous (Intradermal) Reactivity Test	• Drug scaffold: Pass (non-irritating) • Polymer only scaffold: Pass (non-irritating) • Optimized delivery system: Pass (non-irritating)
Systemic Toxicity (Acute)	ISO10993-11:Acute Systemic Toxicity	• Drug scaffold: Pass (non-toxic) • Polymer only scaffold: Pass (non-toxic) • Optimized delivery system: Pass (non-toxic)
	ISO10993-11 and USP <151>: Pyrogen Test (Material Mediated)	• Drug scaffold: Pass (non-pyrogenic) • Polymer only scaffold: Pass (non-pyrogenic) • Optimized delivery system: Pass (non-pyrogenic)
Haemocompatibility	ISO10993-4: Hemolysis Direct and Indirect Contact	• Drug scaffold: Pass (non-hemolytic) • Polymer only scaffold: Pass (non-hemolytic) • Optimized Delivery System: Pass (non-hemolytic)
	ISO10993-4: Coagulation (PT and PPT)	• Drug scaffold: Pass • Polymer only scaffold: Pass • Optimized delivery system: Pass
	ISO10993-4: Complement Activation (C3a and SC5b-9)	• Drug scaffold: Pass • Polymer only scaffold: Pass • Optimized delivery system: Pass

Table IX-1 Biocompatibility Test Summary

Test	Test Description	Test Article and Results
Implantation	ISO10993-11: Subchronic Toxicity- 90day implantation	• Polymer only scaffold: Pass (non- toxic)
Genotoxicity	ISO10993-3: Bacterial Reverse Mutation Assay (AMES Test)	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO10993-3: In Vitro Chromosomal Abberation	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO10993-3: Clastogencity in Mammalian Cells (Forward Mutation)	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)
	ISO10993-3: Mammalian Erythrocyte Micronucleus Test	• Drug scaffold: Pass (non-mutagenic) • Polymer only scaffold: Pass (non-mutagenic)

Since the Absorb GT1 BVS uses the identical drug substance everolimus as XIENCE family of products at the same drug dose density of 100 µg/cm^2, carcinogenicity and teratology studies in the original XIENCE V PMA submission (P070015) were leveraged for the Absorb GT1 BVS. Degradation characterization and impact to biocompatibility were assessed with long term preclinical studies (up to 48 months) in porcine coronary arteries. All the studies met pre-specified study criteria and further support the biocompatibility of the Absorb GT1 BVS.

A2. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with FDA "Guidance for and FDA Staff- Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", April 2010 and "Draft Guidance for Industry, Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies", March 2008, was conducted on the Absorb GT1 BVS System. This testing is summarized in **Table IX-2**. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance documents.

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Scaffold Dimensional and Functional Testing		
Uniformity of Expansion (UOE)	Determines the uniformity of expansion along the scaffold length following nominal deployment.	PASS
Scaffold Percent Length Change	Determines the difference in scaffold length pre-and post-expansion following nominal or post-dilated deployment.	PASS
Percent Recoil	Determines the amount of recoil by which the outer diameters of the scaffold decreases from its expanded diameter on the inflated delivery balloon to its relaxed diameter after deflating the balloon following nominal and post-dilated deployment.	PASS
Circumferential Radial Strength	Determines the radial force or pressure required to permanently deform the deployed scaffold following nominal and post-dilated deployment.	PASS
Radial Stiffness	Determines the radial stiffness of the deployed scaffold following nominal and post-dilated deployment.	For Characterization Only
Inner Scaffold Diameter Prior to Strut Fracture / Post-Dilate to Fracture (PDTF)	Determines the limit for expansion before strut fracture.	PASS
Maximum Crossing Profile Diameter	Determines the crossing profile / crimped scaffold outer diameter.	PASS
Minimum Scaffold Dislodgement Force (Distal)	Determines the minimum force required to dislodge the scaffold from the delivery system in the distal direction.	PASS
Minimum Scaffold Dislodgement Force (Proximal)	Determines the minimum force required to dislodge the scaffold from the delivery system in the proximal direction.	PASS
Nominal Scaffold ID	Determines the scaffold inner diameter (ID) when the device is inflated to nominal balloon pressure.	PASS
Scaffold Markers (Marker Verification)	Verifies the presence of the scaffold markers (marker beads) after subjecting the system to an environment similar to that seen in routine use, including post-dilated deployment.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Visual Inspection / Scaffold Placement	Visually inspects a scaffold and scaffold delivery system and verifies there is no damage to the scaffold and verifies the scaffold placement while in the crimped state.	PASS
Pullback into Guiding Catheter	Determines the ability of the un-deployed system to be withdrawn into a guiding catheter.	PASS
Scaffold Dimensions (Ring Strut Width and Tube Wall Thickness)	Measures dimension tolerances for the uncoated, as cut, pre-sterile scaffold.	PASS
Scaffold Percent Surface Area	Scaffold Percent Surface Area (scaffold-artery ratio) was determined using a theoretical calculation based on the scaffolded vessel area and a 3D computational model of the scaffold design.	For Characterization Only
Radiopacity	Evaluated the ability to visualize the Absorb GT1 BVS System using fluoroscopy during scaffold delivery, deployment, and after implementation.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Magnetic Resonance Imaging (MRI) Safety and Compatibility	Provides confirmation that the Absorb GT1 BVS is safe in the Magnetic Resonance Environment per ASTM F2503-13. Non-clinical testing has demonstrated the Absorb GT1 BVS is MR Conditional. A patient with this device can be safely scanned in all MR environments 3T or less. RF-Induced Heating of Tissue around Absorb GT1 BVS • Experiment data demonstrates that RF-induced heating is minimal. The temperature rise due to RF heating of the Absorb GT1 BVS is similar to that of the background rise with no implant as tested at 1.5T and 3.0T MRI systems per ASTM F2182-11a. • Scientific Rationale indicates that Absorb GT1 BVS has minimal RF-induced heating based on both temperature rise and energy deposition calculations Magnetically Induced Displacement Force • Experiment data demonstrate that the magnetic force measured per ASTM F2052-14 on the Absorb GT1 BVS is minimal • Scientific Rationale indicates that the calculated magnetically induced displacement force on the platinum marker beads is less than its weight in any conceivable (20T) MR system. The marker beads thus meets the safety criterion that magnetic force not exceed the implant weight Magnetically Induced Torque • Experiment data demonstrate that magnetically induced torque on the Absorb GT1 BVS is minimal since force on the Absorb GT1 BVS is not exceed its weight and Absorb GT1 BVS does not move before and after entering magnetic field (3T system). • Scientific Rationale indicates that the calculated worst case torque ratio is 0.256. The torque ratio on the marker beads is less than the gravity value for any conceivable MR system (20T). • Image Artifacts – Experiment data demonstrate that image artifacts on Absorb GT1 BVS is minimal per ASTM F2119-07 (reapproved 2013)	PASS
Scaffold Mechanical Properties	Uniaxial tensile testing was performed to characterize the mechanical properties of PLLA expanded tubing used to manufacture the scaffold.	For Characterization Only

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Longitudinal Scaffold Compression	Determines the total longitudinal scaffold compression when axially loaded.	For Characterization Only
Accelerated Structural Fatigue	Testing was conducted to demonstrate structural durability of the scaffold under expected *in vivo* cyclic loading conditions for an equivalent of 1year (~40 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.	PASS
Delivery System Dimensional and Functional Testing		
Inner Member Lumen Collapse Pressure	Determines if Inner Member (IM) collapse is reversible at negative pressure after inflation to specified pressures for the scaffold delivery systems.	PASS
Balloon Shoulder to Marker Alignment	Determines the distance between the balloon shoulder and marker for the scaffold delivery system.	PASS
Minimum Balloon Working Length	Determines the minimum balloon working length measurement of the scaffold delivery system.	PASS
Guidewire Lumen Dimensions	Measures the guidewire lumen dimensions for the scaffold delivery system.	PASS
Balloon Rated Burst Pressure	Statistically demonstrates with 95% confidence, at least 99.9% of Absorb GT1 BVS Systems will not rupture below the rated burst pressure (RBP).	PASS
Maximum Label Compliance Pressure	Statistically demonstrates with 95% confidence, at least 99% of Absorb GT1 BVS Systems will not rupture below the maximum labeled compliance (MLC) pressure.	PASS
Balloon Fatigue Resistance	Statistically demonstrates with 95% confidence, at least 90% of Absorb GT1 BVS Systems will sustain 10 repeated inflations to the rated burst pressure.	PASS
Balloon Deflation Time	Measures the inflation and deflation time of a balloon from a given pressure.	PASS
Catheter Preparation	Determines the number of double negative aspiration procedures necessary to displace air from the balloon with contract medium.	PASS
Catheter Body and Proximal Adaption Pressure Integrity	Determines the pressure at which the catheter shaft inflation lumen and proximal adaption fail for a scaffold delivery.	PASS
Catheter Flexibility and	Determines the minimum radius of curvature at which the system fails.	PASS

Table IX-2 *In Vitro* Engineering Testing

Test	Test Description	Results
Kink		
Tip Entry Outer Diameter	Measures the entry profile of the scaffold delivery system catheter tip.	PASS

Dimensional Specifications	Measures the catheter dimensions of the scaffold delivery system for:
	• Tip Dimension
	  o Tip Length
	• Mid-Catheter Junction Dimension
	  o Notch OD
	• Shaft Dimensions
	  o Distal Shaft OD
	  o Proximal Shaft OD
	• Proximal Shaft Marker Locations
	  o Femoral Marker
	  o Brachial Marker
	• Catheter Length
	  o Total Catheter Length
	  o Distal Catheter Length
		PASS

Catheter Tensile Strength	Determines the bond strength of a scaffold delivery system at the following locations: Proximal Balloon Seal, Notch Seal / Outer Member to Hypotube Seal, Proximal Adaption, and Soft Tip.	PASS
Hydrophilic Coating (Dry Adhesion)	Determines the adhesion of the hydrophilic coating on the scaffold delivery system shaft.	PASS
Hydrophilic Coating (Coating Coefficient of Friction)	Determines the kinetic coefficient of friction of hydrophilically-coated shafts of the scaffold delivery system.	PASS
Catheter Torque	Determines the rotation number required to break joints and/or materials or to lose functional integrity for the scaffold delivery system.	PASS
Hydrophilic Coating Integrity (Visual Inspection)	A visual assessment of the catheter coating integrity on the surface of the catheters before and after simulated use conditioning of a scaffold delivery system.	For Characterization only
Delivery, Deployment, and Retraction (DDR)	Confirms that the system is able to safely and reliably deliver the scaffold to the intended location according to the instructions for use, without damage to the scaffold.	PASS

A3. Coating Characterization Testing

The coating Characterization testing conducted on the Absorb GT1 BVS System is summarized in **Table IX-3**.

Table IX-3 Coating Characterization Testing

Test	Test Description	Results
Coating Integrity	Determines the percent compromised surface area of the scaffold following post-dilated deployment	PASS
Particulate Matter by Tracking Method	Determines the particulate matter generated during simulated tracking and deployment of the scaffold at RBP.	PASS
Particulate Matter by Beaker Method	Determines the particulate matter generated during deployment and over expansion of the scaffold in a beaker of water.	For Characterization Only
Particulate Matter by Tracking Method (Overlap Configuration)	Determines the particulate matter generated during simulated tracking and deployment of two scaffolds in an overlapped configuration at RBP.	For Characterization Only
Accelerated Embolic and Coating Fatigue (Overlap Configuration)	Testing was conducted to demonstrate coating durability of the Absorb GT1 BVS System under expected *in vivo* cyclic loading conditions for an equivalent of 1 year (~40 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.	For Characterization only
Acute Particulate Chemical Characterization	Testing was conducted to provide chemical characterization for the particulates generated from the system using the particulate matter by tracking method.	For Characterization only
Embolic Fatigue Particulate Chemical Characterization	Testing was conducted to provide chemical characterization for the particulates generated from the scaffold during embolic fatigue characterization.	For Characterization only
Coating Physical Structure and Chemical Properties	Characterizes various aspects of the coated scaffold, including: • Intra-scaffold coating uniformity • Coating adhesion • Coating thickness • Coating morphologies • Coating adhesion after balloon rupture	For Characterization only

A4. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the Absorb GT1BVS System as part of finished product release. This testing is summarized in **Table IX-4**. Information to support the stability of the Absorb GT1 BVS System is summarized separately in **Section IX.A5 Stability/Shelf Life**.

Table IX-4 Absorb GT1 BVS System Analytical Release Testing

Test	Test Description
Appearance	A visual inspection is conducted to verify that the appearance of the Absorb GT1 BVS System meets the specification established for finished product release.
Identity	Assays are conducted to verify the identity of the drug substance, everolimus, on the Absorb GT1 BVS System using two different methods.
Total Content	Assay is conducted to quantitatively verify that the total amount of drug on the Absorb GT1 BVS System meet the specification established for finished product release.
Content Uniformity	Multiple scaffolds are tested to verify that the uniformity of the drug content between individual scaffolds meet the specification established for finished product release.
Degradation Products / Impurities	Assays are conducted to quantitatively verify the amount and type of degradation products / impurities meet the specification established for finished product release.
Particulate Matter *by Tracking Method*	The amount of particulate matter generated during simulated use is verified to meet the specification established for finished product release.
USP <85> Bacterial Endotoxins Test	The amount of bacterial endotoxins is verified to meet the specification established for finished product release.
In Vitro Drug Release	The *in vitro* drug release profile of the drug substance, everolimus, is verified to meet the specification established for finished product release.
Residual Solvent (Acetone)	The amount of residual solvent, acetone, is verified to meet the specification established for finished product release.
Number Average Molecular Weight (M_n)	The number average molecular weight is verified to meet the specification established for finished product release.
Sterility	Product is released by verifying that the dose complied with validated sterilization parameters and satisfies the requirement for labeling the finished product as sterile.
BHT Content	The amount of BHT is verified to meet the specification established for finished product release.

A5. Stability / Shelf Life

A formal stability study was conducted to establish a shelf life / expiration date for the Absorb GT1 BVS System. The stability attributes, including Appearance, Total Content, Degradation Products/ Impurities, Particulate Matter by *Tracking Method, In Vitro* Drug

Release, Number Average Molecular Weight (M_n), Whole Package Integrity Leak Test (bubble test) (in lieu of Sterility), and BHT Content were performed at each of the preselected stability time points. Tests for Identification, Content Uniformity, Residual Solvent (Acetone), and Sterility by Dosimetry were performed for initial lot release only and were not monitored during stability. USP <85> Bacterial Endotoxin Test, required for initial lot release only, was also performed every 6 months for the long-term storage condition (25°C/60%RH) of formal stability study for information purposes only. Testing to establish container closure integrity was conducted to ensure sterility was maintained during the shelf life of the product. Functional testing of the Absorb GT1 BVS System was conducted on aged product. The data generated to-date support a shelf life of 12 months for the Absorb GT1 BVS System.

A6. Sterilization

The Absorb GT1 BVS System is sterilized by means of electron-beam (e-beam) radiation to meet a Sterility Assurance Level (SAL) of 10^{-6} in accordance with EN ISO 11137-1:2006/ Amd1:2013, Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices. Pursuant to the validation requirements, the Absorb GT1 BVS System has been successfully qualified for one time e-beam sterilization. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

B. *In Vivo* Animal Studies

A series of GLP *in vivo* studies were conducted in the porcine coronary artery model in order (a) to evaluate the *in vivo* pharmacokinetic profile, (b) to evaluate the *in vivo* degradation profile, and (c) to demonstrate the *in vivo* safety of the Absorb GT1 BVS System.

This *in vivo* testing was conducted in accordance with one or more of the following general regulations and guidance documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices CDRH. Rockville, MD, 2010
- Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 2005

And the consensus documents:

- Schwartz, R. S., et al. "Drug-Eluting Stents in Preclinical Studies: Updated Consensus Recommendations for Preclinical Evaluation." Circ Cardiovasc Intervent **1**(2): 143-153, 2008.
- Schwartz, R. S., et al. "Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group." Circulation **106**(14): 1867-1873, 2002.

B1. *In Vivo* Pharmacokinetics

Three GLP *in vivo* pharmacokinetics (PK) studies were conducted in porcine coronary arteries in order to determine the *in vivo* PK profile of everolimus for the Absorb GT1 BVS System. The first of these studies includes two PK studies up to 90 days in which consistency in the *in vivo* pharmacokinetics profiles between Absorb BVS (manufactured in Mountain View) and Absorb BVS (manufactured in Temecula) was demonstrated. The third study includes time points up to 300 days, illustrates the complete profile of everolimus elution, and, through biostatistical analysis, demonstrates the bioequivalence in drug elution profiles between the Absorb GT1 BVS and the XIENCE V stent, both of which share the same drug dose density of everolimus (100 $\mu g/cm^2$).

Summary of the *in vivo* PK studies conducted to support product safety are provided in **Table IX-2**.

B2. *In Vivo* Degradation

Three GLP *in vivo* degradation studies were conducted in porcine coronary arteries in order to determine the *in vivo* degradation profile for the Absorb GT1 BVS. These studies are inclusive of time points through 42 months, with results demonstrating complete scaffold resorption by approximately 36 months.

A summary of the *in vivo* degradation studies conducted to support product safety is provided in **Table IX-2**.

B3. *In Vivo* Safety

Seven GLP *in vivo* safety studies were conducted in the porcine coronary artery model in order to demonstrate the *in vivo* safety of the Absorb GT1 BVS. These studies are inclusive of acute (3 days), subchronic (28, 90 days), and chronic (180 days and 12 to 48 months) time points to illustrate the safety of Absorb BVS from implant to beyond complete resorption with multiple interim time points interspersed throughout the resorption period. In addition, two of these seven *in vivo* safety studies were conducted to demonstrate the safety of Absorb GT1 BVS in an overlapping configuration at 28 and 90 days. These studies used XIENCE V (single and overlapping configurations, respectively) as the control article.

A summary of the *in vivo* safety studies conducted to support product safety is provided in **Table IX-2**.

Table IX-2 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Pharmacokinetics R0100315QWB (PK-90a)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 6-7 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60 and 90 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations.
Pharmacokinetics R0110825QWB (PK-90b)	Test: Absorb BVS (mfg TEM) Control: none	Farm swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 7-9 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60 and 90 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations.
Pharmacokinetics R01130812QWB (PK-300)	Test: Absorb BVS (mfg TEM) Control: none	Farm swine and Yucatan mini-swine (n = 3/time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 6-8 scaffolds per time point Control: N/A	3 hours, 1, 3, 7, 14, 28, 60, 90, 180, and 300 days	Characterization of *in vivo* pharmacokinetics: drug release, blood and tissue drug concentrations. Bioequivalence in drug release to XIENCE V.
Polymer Degradation R0100610JCP (D-28)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 5); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 12 scaffolds Control: N/A	28 days	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI
Polymer Degradation R0100223JCP (D-90-180)	Test: Absorb BVS (mfg MTV) Control: none	Farm swine (n = 4, 90 days) and Yucatan mini-swine (n = 6, 180 days); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 12 (90 days), 14 (180 days) scaffolds per time point Control: N/A	90 and 180 days	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI

Table IX-2 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Polymer Degradation R0090623JCP (b) (4)	Test: Absorb BVS (mfg MTV) Control: none	Yucatan mini-swine (n = 3-6 per time point); RCA, LAD, LCX, 1 scaffold per artery with 2-3 scaffolds/ animal	Test: 8 - 12 per time point Control: N/A	12, 18, 24, 30, 36, and 42 months	Characterization of *in vivo* degradation profile with respect to M_n, mass loss, and PDI
Safety R110906JJB (b) (4)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Farm swine (n = 9); RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 12 Control: 9	28 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM • (Histomorphometry, OCT, IVUS)
Safety R110822JJB (b) (4)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Farm swine (n = 10), RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 14 Control: 10	90 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (Histomorphometry, OCT, IVUS)
Safety R110824QWB (b) (4)	Test: Absorb BVS (mfg TEM) Control: XIENCE V	Yucatan mini-swine (n = 9); RCA, LAD, LCX; 1 device/artery; 1-2 test and 1 control/ animal	Test: 12 Control: 9	180 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (Histomorphometry, OCT, IVUS)
Safety R0100222JCP (b) (4)	Test: Absorb BVS (mfg MTV) Control: XIENCE V	Farm swine (n = 7-9, 3, 28, 90 days) and Yucatan mini-swine (n = 9, 180 days); RCA, LAD, LCX, 1 device per artery; 1-2 test and 1 control/ animal	Test: 12 - 14 Control: 7 - 9	3, 28, 90, and 180 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (Histomorphometry, OCT, IVUS)

Table IX-2 GLP *In Vivo* PK, Degradation, and Safety Studies Conducted for the Absorb GT1 BVS System

Study Number (Designation)	Test/Control Articles	Animal Model	Number	Follow-up Duration	Endpoints
Safety R0090622JCP (b) (4)	Test: Absorb BVS (mfg MTV) Control: XIENCE V	Yucatan mini-swine (n = 7-13 per time point); RCA, LAD, LCX, 1 device per artery; 1-2 test and 1 control/ animal	Test: 12-21 Control:7-13	12, 18, 24, 30, 36, 42, and 48 months	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (12 months) (Histomorphometry, OCT, IVUS)
Overlap Safety R0090326JCP (b) (4)	Test: overlapping Absorb BVS (mfg MTV) Control: overlapping XIENCE V	Farm swine (n = 8); RCA, LAD, LCX; 1 OL pair per artery; 1-2 OL test pair and 1 OL control pair/ animal	Test: 12 pairs Control: 8 pairs	28 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (Histomorphometry, OCT)
Overlap Safety R0090325JCP (b) (4)	Test: overlapping Absorb BVS (mfg MTV) Control: overlapping XIENCE V	Farm swine (n = 9); RCA, LAD, LCX; 1 OL pair per artery; 1-2 OL test pair and 1 OL control pair/ animal	Test: 12 pairs Control: 9 pairs	90 days	• Systemic (morbidity / mortality) • Quantitative coronary angiography • Histomorphology • Endothelialization by SEM (Histomorphometry, OCT)

X. SUMMARY OF CLINICAL STUDY

Principal safety and effectiveness information for the Absorb GT1 BVS System is derived from the ABSORB III Randomized Clinical Trial (RCT) and is supported by data from the ABSORB Cohort B clinical trial, ABSORB EXTEND clinical trial, ABSORB II RCT, and ABSORB Japan RCT. In this document, these trials are collectively described as the "ABSORB family of clinical trials" or the "ABSORB trials". These studies evaluated Absorb performance in subjects with ischemic heart disease caused by *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in **Table X-1**.

The clinical investigations outlined in this section were performed on the previous generation Absorb BVS System. The Absorb GT1 BVS has the same mode of expansion, backbone material, scaffold coating, drug density, permanent scaffold markers, and scaffold design as the Absorb BVS. The Absorb GT1 BVS differs from the Absorb BVS only in the scaffold delivery system. The Absorb GT1 scaffold delivery system utilizes the same principle of

operation and materials as other Abbott Vascular RX stent / scaffold systems and coronary dilatation catheters.

Based on the identical nature of the Absorb GT1 scaffold to the Absorb scaffold, performance of the Absorb GT1 BVS can be predicted to be similar to the performance of the Absorb BVS. Within this section, the Absorb BVS and Absorb GT1 BVS System are collectively referred to as "Absorb" and the Absorb BVS and Absorb GT1 BVS are synonymously referred to as the "Absorb scaffold".

ABSORB III RCT is the multi-center (United States and Australia) pivotal trial to support the United States pre-market approval (PMA) of Absorb, and is estimated to register approximately 2262[3] subjects at up to 220 sites. The ABSORB III RCT consists of a prospective, single-blind randomized (2:1 Absorb vs. XIENCE) primary analysis group, a non-randomized lead-in phase, a randomized (1:1 Absorb vs. XIENCE) single-blind imaging cohort, and a non-randomized pharmacokinetics (PK) sub-study (see **Section G - Pharmacokinetics - ABSORB III PK**).

The ABSORB III RCT primary analysis group was designed to evaluate the safety and efficacy of Absorb in the treatment of up to two *de novo* lesions ≤ 24 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. ABSORB III RCT primary analysis group registered 2008 subjects.

Registered subjects were scheduled for clinical follow-up at 30, 180, 360 days and annually from 1 to 5 years. The primary endpoint in the ABSORB III RCT primary analysis group was target lesion failure (TLF, defined as a composite of cardiac death, target vessel myocardial infarction and ischemia-driven target lesion revascularization) at 1 year. Powered secondary endpoints were angina at 1 year, all revascularization at 1 year and ischemia-driven target vessel revascularization (ID-TVR) at 1 year. Lead-in Phase, Imaging Cohort and PK sub-study subjects did not contribute to the primary and powered secondary endpoint analyses. The ABSORB III RCT trial has completed its lead-in and primary endpoint enrollments and yearly follow-up for clinical parameters through 5 years is ongoing.

Twelve subjects were registered in the PK sub-study at 2 sites in the US. All PK subjects have completed their 30-day follow-up and follow-up for clinical parameters through 5 years is ongoing.

The ABSORB Cohort B clinical trial was a prospective, single-arm, open-label, multicenter, international clinical study intended to assess the safety and performance of ABSORB Cohort B Device in the treatment of patients with *de novo* native coronary artery lesions. The ABSORB Cohort B Device is a previous generation of the Absorb GT1 BVS System utilizing a similar Absorb scaffold. A total of 101 subjects were enrolled at 12 clinical sites located in Europe, Australia, and New Zealand. Subjects with up to two *de novo* native coronary artery lesions in separate epicardial vessels with visually estimated nominal vessel

[3] Based on the 4 groups of the ABSORB III trial: primary analysis, lead-in, imaging and PK.

diameters of 3.0 mm and lesion(s) length ≤ 14 mm were enrolled, and received a single 3.0 x 18 mm Absorb per lesion treated.

Subjects were evaluated at 30 days, 180 days, 270 days, 12 months, 18 months (subset), 2 years, 3 years, 4 years and 5 years. Subjects in the first group (B1) had invasive imaging with qualitative coronary angiography, IVUS, IVUS-VH, and OCT at 6 months, 2 years and 5 years while the second group (B2) had these invasive imaging at 12 months, 3 years and 5 years. Vasomotor function test using nitroglycerin was done at 2, 3 and 5 year follow-up. A MSCT scan was mandatory for a subset of subjects at 18 months and at 5 years.

The ABSORB EXTEND trial was established to expand treatment with Absorb in a broader patient population around the world (outside of the USA), to collect clinical data with minimum follow-up imaging, and to increase lesion complexity by including subjects with longer lesions treated with either overlapping of two Absorb or use of longer length Absorb.

ABSORB EXTEND was a prospective, non-randomized single arm, open-labeled multi-center clinical trial registering subjects with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels; target lesions were ≤ 28 mm in length with RVD ≥ 2.0 mm to ≤ 3.3 mm. Target lesions > 22 mm were to be treated with overlapping of two Absorb scaffolds. This clinical trial registered 812 subjects at 56 sites. The ABSORB EXTEND trial was to continue the assessment of the safety and performance of Absorb with no primary endpoint established for hypothesis testing. Key clinical endpoints include: Acute success; Major Adverse Cardiac Event (MACE), Target Vessel Failure (TVF) and their components at each follow-up. All subjects have completed their 1-year follow-up; 2-year and 3-year follow-ups are ongoing.

The ABSORB II RCT is the CE mark post-approval randomized clinical trial designed to compare the safety, efficacy and performance of Absorb compared to XIENCE in the treatment of *de novo* native coronary artery lesions.

The ABSORB II RCT is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial (Europe and New Zealand) registering 501 subjects at 46 sites. Target lesions were up to 2 *de novo* native coronary artery lesions, each located in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 mm and 3.8 mm as estimated by on-line quantitative coronary angiography (QCA), and a lesion length of ≤ 48 mm. Planned overlapping of study devices was allowed for treatment of long lesions. The co-primary endpoints of the study are vasomotor function assessed by change in mean lumen diameter between pre- and post-nitrate at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both by angiography. Follow-up through 1 year is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The ABSORB Japan RCT is the randomized pivotal trial for Japan approval of Absorb that evaluates safety and effectiveness of Absorb in the treatment of subjects with ischemic heart disease caused by *de novo* native coronary artery lesions in a Japanese population in comparison to XIENCE. The ABSORB Japan RCT is a prospective, randomized (2:1

Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial in Japan registering 400 subjects at 38 investigational sites. Treated lesions were up to 2 *de novo* native coronary artery lesions, each located in different major epicardial vessels, with D_{max} between ≥ 2.5 mm and ≤ 3.75 mm and lesion length of ≤ 24 mm, by visual estimation. Planned overlapping treatment of the target lesion was not allowed. If a subject had only one target lesion eligible to be treated with the study device, the additional non-target lesion could be treated with XIENCE. The primary endpoint of the study is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year, non-inferiority against the control. All subjects have completed their 1-year follow-up, and follow-up through 5 years is ongoing.

This clinical section presents one-year outcomes for ABSORB III RCT, ABSORB Cohort B, ABSORB EXTEND, ABSORB II RCT, and ABSORB Japan RCT.

Table X-1 Overview of ABSORB Family of Clinical Trials

	ABSORB III RCT	ABSORB Cohort B	ABSORB EXTEND	ABSORB II RCT	ABSORB Japan RCT
Study Design	Multi-center Randomized (2:1) Single-blinded Active-Control	Multi-center Non-randomized First-in-man	Multi-center Non-Randomized Continued Assessment	Multi-center Randomized (2:1) Single-blinded Active-Control	Multi-center Randomized (2:1) Single-blinded Active-Control
Numbers of Patients	Total: 2008 primary analysis population Absorb: 1322 XIENCE Control: 686	Total: 101 Group1: 45 Group 2: 56 All Absorb	Total: 812 All Absorb	Total: 501 Absorb: 335 XIENCE Control: 166	Total: 400 Absorb: 266 XIENCE Control: 134
Numbers of Enrolling Sites	193 sites for primary endpoint analysis population	12 sites	56 sites	46 sites	38 sites
Study Geography	US and AUS	AUS, EU, NZ	AP, EU, CA, BZ	EU, NZ	JN
Vessel Sizes and Lesion Lengths	RVD: $\geq$ 2.5 and $\leq$ 3.75 mm Length: $\leq$ 24 mm	RVD: 3.0 mm Length: $\leq$ 14 mm	$D_{max} \geq$ 2.0 mm and $D_{max} \leq$ 3.3 mm Length: $\leq$ 28 mm	$D_{max} \geq$ 2.25 mm and $\leq$ 3.8 mm Length: $\leq$ 48 mm	$D_{max} \geq$ 2.25 mm and $\leq$ 3.75 mm, Length: $\leq$ 24 mm
# of Lesion Allowed	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed	Up to two *de novo* lesions in different epicardial vessels. Planned overlap allowed.	Up to two *de novo* lesions in different epicardial vessels. Planned overlap allowed.	Up to two *de novo* lesions in different epicardial vessels. No planned overlap allowed.
Scaffold/Stent Sizes	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 12, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 12, 18, 28 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 12, 18, 28 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 12, 18, 28 mm
Primary Endpoint(s)	One-year TLF (non-inferiority)	None	None	• Change in Mean Lumen Diameter from pre- to post-nitrate at 2 years (superiority) • Change in Minimum Lumen Diameter (MLD) at 2 years post-nitrate minus MLD post procedure post-nitrate (non-inferiority, reflex to superiority)	One-year TLF (non-inferiority)

	ABSORB III RCT	ABSORB Cohort B	ABSORB EXTEND	ABSORB II RCT	ABSORB Japan RCT
Major Secondary Endpoints	• Angina (powered) • Target Vessel Revascularization (powered) • All revascularization (powered) • Diabetic indication (powered) • Imaging endpoint (powered)	None	None	None	• Late loss at 13 months • Vaso-reactivity at 3-years • Change in MLD at 3-years
Post Procedure Antiplatelet Therapy	Clopidogrel, prasugrel or ticagrelor 12 months minimum (or ticlopidine per site standard). Aspirin for 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard). Aspirin for 5 years.	Clopidogrel, prasugrel or ticagrelor 6 months minimum (or ticlopidine per site standard). Aspirin for 3 years	Clopidogrel, prasugrel or ticagrelor 6 months minimum (or ticlopidine per site standard). Aspirin for 5 years	Clopidogrel or prasugrel 12 months minimum (or ticlopidine per site standard). Aspirin indefinitely.
Clinical follow-ups	30, 180 days, annually 1 to 5 years	30, 180, 270 days, annually 1 to 5 years	30, 180 days, annually 1 to 3 years	30, 180 days, annually 1 to 5 years	30, 180 days, annually 1 to 5 years
Angiographic Follow-up	3 years*	Group 1: 180 days, 2 years and 5 years (n=45) Group 2: 1 year, 3 years, and 5 years (n=56)	Post-procedure and 2 years*	2 years	13 months, 2 to 4 years*
IVUS and/or OCT Follow-up	3 years*	Group 1: 180 days, 2 years and 5 years(n=45) Group 2: 1 year, 3 years and 5 years (n=56)	Post-procedure and 2 years*	2 years	2 to 3 years*
MSCT Follow-up	None	18 months	18 months*	3 years	13 months and 3 years*
CTA/SPECT	N/A	N/A	N/A	N/A	N/A
PK Study	Yes (12 subjects; US)	None	None	None	None
Status	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing.	Completed enrollment and follow-up.	Completed enrollment. Follow-up through 1 year completed. Follow-up through 3 years ongoing.	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing	Completed enrollment. Follow-up through 1 year completed. Follow-up through 5 years ongoing.

AP, Asia Pacific; AUS, Australia; BZ, Brazil; CA, Canada; EU, Europe; JN, Japan; NZ, New Zealand; US, the United States of America
* Imaging sub-group

A. ABSORB III Randomized Controlled Trial

A1. Study Design

The ABSORB III Randomized Controlled Trial (ABSORB III) is a prospective, multi-center trial, registering approximately 2262 subjects. The primary objective of ABSORB III is to evaluate the safety and effectiveness of Absorb compared to XIENCE in the treatment of subjects, including those with diabetes mellitus, with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. The ABSORB III trial includes the following 4 groups:

Lead-in Group (≤ 50 subjects)

A non-randomized group to evaluate the applicability and transferability of the didactic Absorb physician training plan to United States (US) clinical practice in up to 50 subjects. The registration of the ABSORB Lead-in subjects began on December 28, 2012 and was completed on April 1, 2013 with a total of 24 subjects.

Primary Analysis Group (~2000 subjects)

This is a randomized group (2:1 Absorb to XIENCE) designed with the primary endpoint to support US approval of Absorb showing non-inferiority of Absorb compared to XIENCE in 1-year target lesion failure (TLF). The first randomized subject was treated on March 22, 2013 and the last subject was treated on April 3, 2014 for a total of 2008 primary analysis subjects.

Imaging Cohort (~200 subjects)

A randomized (2:1 Absorb to XIENCE) sub-study to evaluate long-term vascular function and patency of Absorb treated segments compared to XIENCE treated segments in the treatment of subjects with ischemic heart disease caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels. Enrollment is currently ongoing.

Pharmacokinetic (PK) Group (~12 subjects)

A prospective, open-label, unblinded sub-study to determine the pharmacokinetics of everolimus delivered by the Absorb in a separate and non-randomized group of subjects who only receive Absorb with a maximum of two *de novo* native coronary artery lesions after implantation of Absorb. (Note: The ABSORB III PK subjects will not contribute to the determination of the ABSORB III primary endpoint.) The first PK subject was treated on June 2, 2014 and the last/12th PK subject was treated on September 17, 2014.

Results from the ABSORB III primary analysis group are presented in this section and results from the pharmacokinetic analysis can be found in **Section G - Pharmacokinetics - ABSORB III PK**.

The primary endpoint for ABSORB III primary analysis group is target lesion failure (TLF) at 1-year, a composite endpoint of cardiac death, myocardial infarction attributable to target vessel (TV-MI) or ischemia-driven target lesion revascularization (ID-TLR).

The ABSORB III trial is powered based on the primary endpoint of TLF. The results presented in this clinical section are based on the intention-to-treat (ITT) populations of Absorb and XIENCE arms. The 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.

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

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

TLF_{Absorb} and TLF_{XIENCE} are the 1-year TLF rates in the Absorb and XIENCE arms, respectively. Δ_{PE} is the non-inferiority margin for the primary endpoint (4.5%).

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

Clinical Inclusion / Exclusion Criteria

Subjects with symptomatic myocardial ischemia who have a maximum of two *de novo* native coronary artery lesions in separate epicardial vessels, who meet all eligibility criteria and provided written informed consent were registered in the trial. Subjects were male or female and had to be at least 18 years old and suitable for PCI. Female subjects with childbearing potential had to have a negative pregnancy test within 7 days of the index procedure.

Angiographic Inclusion Criteria

Key angiographic inclusion criteria included: lesion located in native coronary artery with RVD ≥ 2.5 mm and ≤ 3.75 mm by visual estimation and lesion length of ≤ 24 mm by visual estimation; visually estimated or quantitatively assessed % diameter stenosis (DS) of ≥ 50%; TIMI flow ≥ 1.

Key angiographic exclusion criteria included: lesion in left main or aorto-ostial RCA lesion (within 3 mm of ostium); excessive tortuosity (≥ two 45° angles) proximal to or within the target lesion; extreme angulation (≥ 90°) proximal to or within the target lesion; moderate or heavy calcification proximal to or within the target lesion; target vessel containing thrombus; lesion involving a bifurcation with side branch ≥ 2 mm in diameter, or side branch with either an ostial or non-ostial lesion with diameter stenosis > 50%, or side branch requiring dilatation.

Medication and Follow-Up

Subjects selected were required to receive a loading dose of ≥ 300 mg of aspirin within 24 hours prior to index procedure, regardless of whether the patient was previously taking aspirin. Subjects were also required to receive a loading dose of a P2Y12 receptor antagonist within 24 hours prior to index procedure (preferred), but in all cases no greater than 1 hour after the end of the procedure. Subjects were required to receive dual antiplatelet therapy for 1 year after the index procedure.

Clinical follow-up in the ABSORB III is required at the following intervals for all subjects: 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.

Clinical Endpoints

The ABSORB III primary endpoint was TLF at 1 year, defined as the composite of: cardiac death, myocardial infarction attributable to target vessel (TV-MI) or ischemia-driven target lesion revascularization (ID-TLR).

Powered secondary endpoints were:

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

Other key secondary endpoints to examine the safety and efficacy of Absorb are listed below.

Components:

- Death (cardiac, vascular, non-vascular)
- Myocardial infarction attributable to target vessel (TV-MI), or not attributable to target vessel (NTV-MI)
- Ischemia-driven or non-ischemia-driven TLR (ID-TLR, NID-TLR)
- Target vessel revascularization (ID-TVR, non ID-TVR)

Composite Endpoints:

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

Scaffold / Stent Thrombosis (per ARC Definition):

- Timing (acute, sub-acute, late and very late)
- Evidence (definite and probable)

A2. Accountability of Subjects

In ABSORB III, a total of 2008 (Absorb: 1322; XIENCE: 686) patients were randomized at 193 study sites, between March 22, 2013 and April 3, 2014. A total of 1385 lesions were treated in the Absorb arm, and 713 in the XIENCE arm. Early termination evaluated at 365 days, due to lost to follow-up, consent withdrawal or death, affected 1.7% (23/1322) of the subjects in the Absorb arm and 1.6% (11/686) in the XIENCE arm. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

A3. Study Population Demographics and Baseline Parameters

The key baseline demographics and risk factors for the primary analysis group, ITT population, of ABSORB III are shown in **Table X-2**. All baseline characteristics were balanced with no statistical differences between the study arms. The mean age was 63.5 ± 10.6 years in the Absorb arm and 63.6 ± 10.3 years in the XIENCE arm. Risk factors having a high prevalence in Absorb and XIENCE arms included hypertension requiring medication (81.0% (1071/1322) and 80.6% (553/686), respectively) and dyslipidemia requiring medication (76.3% (1009/1322) and 77.7% (533/686), respectively). All diabetes mellitus comprised 31.5% (416/1320) and 32.7% (224/686), respectively, and insulin-required diabetes mellitus subjects comprised 10.5% (138/1320) and 11.2% (77/686), respectively. Among diabetics, HbA1c levels for Absorb and XIENCE arms were 7.56 ± 1.76% and 7.78 ± 2.06%, respectively. Mean body mass index values were 30.58 ± 6.22 and 30.47 ± 6.26, respectively, indicating an overall obese population. For cardiac status, the most common disease presentation in Absorb and XIENCE arms was stable angina (57.3% (757/1321) and 60.8% (417/686), respectively). Subjects with a single diseased artery were most prevalent in the ABSORB III population (69.5% (919/1322) and 67.2% (461/686), respectively).

Table X-2 ABSORB III Key Baseline Patient Characteristics and Risk Factors – Per-Subject Analysis (Primary Analysis Group, Intent-To-Treat Population)

	Absorb (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
Subject Background			
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] By normal approximation for continuous variables and Newcombe score method for binary variables

A4. Safety and Efficacy Results

The primary analysis of TLF at 1 year was in the ITT population and is shown below in **Table X-3**. The TLF rate at 1 year was 7.8% (102/1313) in the Absorb arm and 6.1% (41/677) in the XIENCE arm. The difference between the two treatment arms was 1.71% with the 97.5% upper confidence limit being 3.93%, which was less than the non-inferiority margin of 4.5%. The Absorb arm was non-inferior to XIENCE with a non-inferiority p-value of 0.0070 for observed TLF rates at 1 year.

Table X-3 ABSORB III Primary Endpoint Analysis (Primary Analysis Group - Intent-to-Treat Population, Per-Protocol MI Definition)

	Absorb (N=1322)	XIENCE (N=686)	Difference (Upper One-Sided 97.5% CL[1])	Non-Inferiority P-Value[2]
1-Year TLF (Cardiac Death Target Vessel MI, ID-TLR)	7.8% (102/1313)	6.1% (41/677)	1.71% (3.93%)	0.0070

[1] One-sided upper 97.5% confidence limit by Farrington-Manning method

[2] One-sided p-value by using Farrington-Manning non-inferiority test statistic with non-inferiority margin of 4.5%, to be compared with a one-sided significance level of 0.025

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Note: MI is per ABSORB III protocol definition

The analyses of Angina, All Revascularization and ID-TVR at 1 year for the ITT population are shown in **Table X-4**. Superiority was not met for any of the powered secondary endpoints. Clinical results are presented in **Table X-5**.

Table X-4 ABSORB-III Powered Secondary Endpoints (Primary Analysis Group - Intent-to-Treat Population)

	Absorb (N=1322)	XIENCE (N=686)	Difference [95% CL][4]	Superiority P-Value[5]
Powered Secondary Endpoint				
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%]	0.5040
1-Year ID-TVR[3]	5.0% (66/1313)	3.7% (25/677)	1.33% [-0.51%, 3.18%]	0.2126

[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] For the powered secondary endpoint of Angina, Pearson's Chi-square two-sided 95% confidence interval. For the powered secondary endpoints of All Revascularization and ID-TVR, exact two-sided 95% confidence interval.

[5] To be compared with a two-sided significance level of 0.05. For the powered secondary endpoint of Angina, two-sided p-value by using Pearson's Chi-square test statistic. For the powered secondary endpoints of All Revascularization and ID-TVR, two-sided p-value by using Fisher's exact test statistic.

Note: 1-year timeframe includes a window of ± 28 days

Note: N is the total number of subjects

Table X-5 ABSORB-III Clinical Results (Primary Analysis Group - Intent-to-Treat Population) - 1-Year Results

	Absorb (N=1322)	XIENCE (N=686)	Difference [95% CI][1]
COMPOSITE EFFICACY AND SAFETY			
TLF	7.8% (102/1313)	6.1% (41/677)	1.71% [-0.74%, 3.93%]
EFFICACY			
Ischemia-Driven TLR	3.0% (40/1313)	2.5% (17/677)	0.54% [-1.14%, 1.96%]
TLR, CABG	0.2% (3/1313)	0.4% (3/677)	-0.21% [-1.08%, 0.31%]
TLR, PCI	2.8% (37/1313)	2.2% (15/677)	0.60% [-1.00%, 1.96%]
Ischemia-Driven TVR	5.0% (66/1313)	3.7% (25/677)	1.33% [-0.67%, 3.10%]
SAFETY			
All Death	1.1% (15/1313)	0.4% (3/677)	0.70% [-0.26%, 1.49%]
Cardiac Death	0.6% (8/1313)	0.1% (1/677)	0.46% [-0.29%, 1.06%]
Vascular Death	0.2% (2/1313)	0.0% (0/677)	0.15% [-0.42%, 0.55%]
Non-cardiovascular Death	0.4% (5/1313)	0.3% (2/677)	0.09% [-0.72%, 0.64%]
All MI (Per Protocol Definition)	6.9% (90/1313)	5.6% (38/677)	1.24% [-1.11%, 3.36%]
TV-MI	6.0% (79/1313)	4.6% (31/677)	1.44% [-0.74%, 3.39%]
QMI	0.7% (9/1313)	0.3% (2/677)	0.39% [-0.45%, 1.04%]
NQMI	5.3% (70/1313)	4.3% (29/677)	1.05% [-1.06%, 2.91%]
NTV-MI	0.8% (11/1313)	1.2% (8/677)	-0.34% [-1.54%, 0.53%]
QMI	0.1% (1/1313)	0.1% (1/677)	-0.07% [-0.76%, 0.30%]
NQMI	0.8% (10/1313)	1.0% (7/677)	-0.27% [-1.41%, 0.56%]
Cardiac Death or MI	7.5% (98/1313)	5.8% (39/677)	1.70% [-0.70%, 3.87%]
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-393 days)	1.54% (20/1301)	0.74% (5/675)	0.80% [-0.32%, 1.72%]
Acute (≤ 1 day)	0.15% (2/1320)	0.58% (4/686)	-0.43% [-1.34%, 0.10%]
Sub-Acute (> 1-30 days)	0.91% (12/1315)	0.15% (1/686)	0.77% [-0.01%, 1.45%]
Late (31-365 days)	0.46% (6/1299)	0.00% (0/675)	0.46% [-0.16%, 1.00%]
Very Late (> 365-393 days)	0.00% (0/1299)	0.00% (0/675)	0.00% [-0.57%, 0.29%]

[1] By Newcombe score method
Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition

Analysis Stratified by Reference Vessel Diameter (RVD) Size

In the ABSORB III trial, the pre-procedure RVD defined in the protocol was ≥ 2.5 mm to ≤ 3.75 mm by visual estimation/site assessment. With Absorb being a slightly larger device compared to XIENCE, a post-hoc analysis by RVD was conducted using the RVD cut-off of ≥ 2.25 mm versus < 2.25 mm (by QCA). The 2.25 mm cut-off was chosen based on the lower bound RVD criteria in the ABSORB III trial being 2.5 mm and QCA's underestimation of visual assessment by ~0.25 mm. **Table X-6** provides the key clinical results by the RVD subgroups of ≥ 2.25 mm (by QCA) and < 2.25 mm (by QCA). In the ABSORB III trial, 81% of the population had a RVD ≥ 2.25 mm (by QCA). In RVD ≥ 2.25 mm (by QCA) subgroup, both the Absorb and XIENCE arms performed similarly to the overall ABSORB III population. In the RVD ≥ 2.25 mm (by QCA) subgroup, the TLF rate was low and similar between Absorb (6.7%) and XIENCE (5.5%). The TLF rates in the overall population were 7.8% for Absorb and 6.1% for XIENCE. The difference between the two arms was less in the RVD ≥ 2.25 mm (by QCA) subgroup than that in the overall ABSORB III population (1.2% vs. 1.7%, respectively). Additionally, in the RVD ≥ 2.25 mm (by QCA) subgroup, the ST rate was low and similar between Absorb (0.9%) and XIENCE (0.6%) and the difference in ST between the two arms was less than that in the overall ABSORB III population (0.3% vs. 0.8%, respectively).

Table X-6 also presents the clinical outcomes for the subgroup with pre-procedure RVD < 2.25 mm (by QCA). Although visually estimated by investigators to be ≥ 2.5 mm, subjects with RVD < 2.25 mm (by QCA) made up 19% of the overall ABSORB III population. The event rates were higher in both the Absorb and the XIENCE arms in the RVD < 2.25 mm (by QCA) subgroup, as compared to both the overall ABSORB III population and RVD ≥ 2.25 mm (by QCA) subgroup.

Table X-6 Clinical Results for ABSORB III Stratified by Pre-Procedure RVD Size - RVD ≥ 2.25 mm and RVD < 2.25 mm by QCA (ITT population) – 1-Year Results

	Subjects with RVD ≥ 2.25 mm		Subjects with RVD < 2.25 mm*	
	Absorb (N=1074)	**XIENCE (N=549)**	**Absorb (N=242)**	**XIENCE (N=133)**
Percentage of Subjects	81.6% (1074/1316)	80.5% (549/682)	18.4% (242/1316)	19.5% (133/682)
Pre-procedure Median RVD by QCA (mm) Range (min, max)	2.75 (2.25, 4.04)	2.72 (2.26, 4.48)	2.08 (1.39, 3.54)	2.10 (1.46, 3.49)
TLF	6.7% (71/1067)	5.5% (30/542)	12.9% (31/241)	8.3% (11/133)
Cardiac Death	0.6% (6/1067)	0.2% (1/542)	0.8% (2/241)	0.0% (0/133)
TV- MI	5.2% (55/1067)	4.6% (25/542)	10.0% (24/241)	4.5% (6/133)
ID-TLR	2.2% (24/1067)	1.5% (8/542)	6.6% (16/241)	6.8% (9/133)
Stent/Scaffold Thrombosis (Def/Prob)	0.9% (9/1058)	0.6% (3/540)	4.6% (11/238)	1.5% (2/133)

Note: N is the total number of subjects

Note: MI is per protocol definition

* The ITT subjects with at least one target lesion pre-procedure RVD < 2.25 mm (core-lab measurement) are included in the analysis.

B. Analysis of Diabetic Subjects in ABSORB III

The diabetic patient population is at high risk for cardiovascular morbidity and mortality and is associated with worse clinical outcomes when undergoing PCI. In the ABSORB III trial, diabetic patients represented 31.9% (640/2006) of the overall trial population. The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent/scaffold thrombosis for the overall population, all diabetes mellitus (all DM) subgroup and all non-DM subgroup are shown in **Table X-7**.

For the all DM subgroup, the observed clinical event rates in both Absorb and XIENCE arms were higher than in the overall population and non-DM subgroup for most key outcome measures. For most endpoints, the % increase in event rates from the overall population to the diabetic population is similar between the two arms. For the all non-DM subgroup, the observed clinical event rates in both arms were lower than in the overall population for most key outcome measures. The only exception to this pattern was in cardiac death, which in

both arms was nearly unchanged between the overall population and both subgroups. For the DM subgroup, non-DM subgroup, and the overall population, there were no statistical differences for any endpoint comparisons between study arms.

Table X-7 Subgroup Information and 1-Year Clinical Outcomes Stratified by Diabetic Status – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)

	All DM		All non-DM	
	Absorb (N=416)	**XIENCE (N=224)**	**Absorb (N=904)**	**XIENCE (N=462)**
TLF	10.7% (44/411)	9.1% (20/220)	6.3% (57/900)	4.6% (21/457)
Cardiac Death	0.5% (2/411)	0.0% (0/220)	0.7% (6/900)	0.2% (1/457)
TV- MI	9.0% (37/411)	7.3% (16/220)	4.6% (41/900)	3.3% (15/457)
ID-TLR	5.6% (23/411)	3.6% (8/220)	1.8% (16/900)	2.0% (9/457)
Stent/Scaffold Thrombosis (Def/Prob)	3.2% (13/405)	1.4% (3/219)	0.8% (7/894)	0.4% (2/456)

The Absorb arm of the diabetic subgroup had a higher observed 1 year stent / scaffold thrombosis rate compared to XIENCE. Further analysis identified that approximately 70% of the ST in both arms occurred in very small vessels (< 2.25 mm), outside of the intended indication. In the ≥ 2.25 mm subgroup, device thrombosis rates were 1.3% for Absorb (4/318) and 0.6% for XIENCE (1/173).

C. ABSORB Cohort B

The ABSORB Cohort B trial continued the clinical evaluation of the feasibility and performance of the Absorb BVS System (ABSORB Cohort B device) in the treatment of single *de novo* native coronary artery lesion. The ABSORB Cohort B Device is a previous generation of the Absorb GT1 BVS System utilizing a similar Absorb scaffold.

C1. Study Design

The ABSORB Cohort B trial was a prospective, non-randomized single arm, open-labeled multi-center clinical trial, with plans to register approximately 80 subjects. Due to immense physician interest, enrollment was completed at 101 patients. The Cohort B was subdivided into two subgroups and different imaging follow-up schedules were applied.

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 18 years of age and had evidence of myocardial ischemia (stable or unstable angina, or silent ischemia). Female subjects with childbearing potential had to have a negative pregnancy test within 7 days prior to the index procedure. The subjects who were considered eligible based on the general inclusion and exclusion criteria were invited to enroll in the study and provided written informed consent. The final assessment for eligibility for subject registration was conducted based on pre-procedure angiographic results.

Key angiographic inclusion criteria included: Nominal vessel diameter of 3.0 mm; lesion length ≤ 14 mm; % diameter stenosis (%DS) of ≥ 50% and < 100%; TIMI flow of ≥ 1. Key angiographic exclusion criteria included: 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.

Percutaneous coronary intervention (PCI) for other lesions in a non-target vessel could be done ≥ 90 days prior to or if planned to be done 6 months after the index procedure. PCI for other lesions in the target vessel could be done > 6 months prior to or if planned to be done 6 months after the index procedure.

Medication and Follow-Up

All subjects were required to receive anticoagulation and other therapy during stent implantation according to the standard of care at the clinical site. 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). Subjects who developed sensitivity to clopidogrel bisulfate were to be switched to ticlopidine hydrochloride at a dose in accordance with standard hospital practice.

Subjects were evaluated at 30 days, 180 days, 270 days, 12 months, 18 months (subset), 2 years, 3 years, 4 years and 5 years. Subjects in the first group (B1) had invasive imaging with qualitative coronary angiography, IVUS, IVUS-VH, and OCT at 6 months, 2 years and 5 years while the second group (B2) had these invasive imaging at 12 months, 3 years and 5 years. Vasomotor function test using nitroglycerin was done at 2, 3 and 5 year follow-up. A MSCT scan was mandatory for subset of subjects at 18 months and at 5 years.

Clinical Endpoints

The Absorb Trial Cohort B was an exploratory trial and the primary endpoint for hypothesis test was not set. Key endpoints include: 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.

C2. Accountability of Subjects

The ABSORB Trial Cohort B registered 101 subjects (Group B1: 45, Group B2: 56) in 12 clinical sites (3 sites in The Netherlands, 2 sites in Australia, 2 sites in New Zealand, 1 site in Belgium, 1 site in Denmark, 1 site in France, 1 site in Poland and 1 site in Switzerland), between March 9, 2009 and November 6, 2009.

C3. Study Population Demographics and Baseline Parameters

A total of 101 subjects are included in the analysis for the full Cohort B (45 subjects in Group 1 and 56 subjects in Group 2). The mean age of the full Cohort B subjects (ITT population) was 62.26 ± 8.93 years. 72.3% of subjects were men and 17.0% of subjects were current smoker. Diabetic subjects compromised 16.8% of the overall population. 66.0% of subjects had hypertension and 85.1% of subjects had hypercholesterolemia. 54.6% had a family history of coronary artery disease. 25.0% of subjects had prior MI and 6.9% of subjects had a prior cardiac intervention on target vessel. 14.9% of subjects presented with unstable angina at the time of index procedure. There were 20.8% subjects who had multi-vessel disease.

The lesions treated in the full Cohort B subjects (ITT population) are primarily located in LAD (43.1%). According to the ACC/AHA classification, there were 40% type B2 and 4% type C lesions. Based on QCA measurement, the mean lesion length was 9.92 ± 3.65 mm and the mean reference vessel diameter was 2.61 ± 0.37 mm. Pre-procedure MLD was 1.06 ± 0.28 mm and % diameter stenosis was 58.99 ± 10.00%.

C4. Safety and Efficacy Results

The clinical results are presented in **Table X-8**, below. Clinical results are presented through 5 years. For the full Cohort B (ITT population), the MACE rate was 6.9% (7/101) at 1 year (3 NQMI and 4 ID-TLR) and 11.0% (11/100) at 5 years (3 NQMI and 8 ID-TLR).

Table X-8 Key Clinical Outcomes of ABSORB Cohort B (ITT Population) through 5 years

	Absorb 30 days (N=101)	Absorb 6 months (N=101)	Absorb 1 year (N=101)	Absorb 2 year (N=100*)	Absorb 3 year (N=100*)	Absorb 4 year (N=100*)	Absorb 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 per protocol definition
Note: Follow-up windows were: 30 days ± 7 days; 6 months ± 14 days; 1 year ± 28 days; 2 year ± 2 months; 3 year ± 28 days; 4 year ± 28 days; 5 year ± 28 days

C5. Imaging and Vasomotor Function Results

Intravascular Ultrasound (IVUS) Outcomes

Cohort B1: Paired IVUS data at post-procedure, 6-month, 2-year, and 5-year follow-up were available for 21 lesions from Group 1 subjects (**Table X-9**). Average plaque area increased significantly from post-procedure to 6 months (7.81 mm^2 to 8.33 mm^2, p = 0.0140). However, the average vessel, lumen and scaffold area remained comparable between baseline and 6 months. From 6 months to 2 years there were significant increases in vessel area (14.92 mm^2 to 15.88 mm^2, p = 0.0009) and scaffold area (6.63 mm^2 to 7.52 mm^2, p < 0.0001). These enlargements were accompanied by late increased average lumen area (6.59 mm^2 vs. 7.24 mm^2, p = 0.0153). These results indicate a late lumen expansion with Cohort B Device implantation. At 5 years, scaffold area was no longer identifiable from IVUS imaging. There was a significant reduction in plaque area from 2 to 5 years (8.64 mm^2 vs.

7.75 mm^2, p = 0.0005), but the average lumen area remained stable (7.24 mm^2 vs. 7.46 mm^2, p = 0.2774).

Table X-9 Paired IVUS Results at Post-procedure, 6 Month, 2 Year, and 5 Year (Group 1, ITT Population)

	Post-procedure (L = 21)	6-Month (L = 21)	2-Year (L = 21)	5-Year (L = 21)	p-value (post vs 6M)*	p-value (6M vs 2Y)*	p-value (2Y vs 5Y)*
Average 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
Average scaffold area (mm^2)	6.75 ± 1.19	6.63 ± 1.16	7.52 ± 1.79	NA	0.1754	< 0.0001	NA
Average 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
Average 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

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

Cohort B2: Paired IVUS data at post-procedure, 1-year, 3-year, and 5-year follow-up were available for 30 lesions from Group 2 subjects (**Table X-10**). There was a modest but significant increase in total plaque area (7.30 mm^2 to 7.84 mm^2, p = 0.0095) with concomitant non-significant increase in vessel area. Average scaffold and lumen area remain unchanged through 1 year. From 1 to 3 years, both scaffold area and lumen area increased significantly (6.37 mm^2 vs. 7.05 mm^2, p < 0.0001; and 6.31 mm^2 vs. 6.70 mm^2, p = 0.0028, respectively). The late lumen enlargement is of particular interest because the vessel area was preserved (14.15 mm2 at 1 year vs. 14.25 mm2 at 3 years, p = 0.4560). The late lumen enlargement observed by IVUS from 1 year to 3 years in Group 2 is consistent with the trends noted previously between 6 months and 2 years in Group 1 and reinforces the unique properties of the bioresorbable scaffold. At 5 years, scaffold area was no longer identifiable from IVUS imaging. The average vessel area and plaque area decreased from 3 to 5 years, and the average lumen area remained comparable to that at 3 years (6.48 mm^2 vs. 6.70 mm^2, p = 0.1838).

Table X-10 Paired IVUS Results at Post-procedure, 1, 3, and 5 Year (Group 2, ITT Population)

	Post-procedure (L = 30)	1-Year (L = 30)	3-Year (L = 30)	5-Year (L = 28)	p-value (post vs 1Y)*	p-value (1Y vs 3Y)*	p-value (3Y vs 5Y)*
Average Vessel Area (mm^2)	13.61 ± 2.40	14.15 ± 2.61	14.25 ± 2.57	13.23 ± 2.70	0.0629	0.4560	0.0003
Average Scaffold Area (mm^2)	6.31 ± 0.86	6.37 ± 0.97	7.05 ± 1.39	NA	0.8646	< 0.0001	NA
Average Lumen Area (mm^2)	6.31 ± 0.86	6.31 ± 1.01	6.70 ± 1.48	6.48 ± 1.50	0.4199	0.0028	0.1838
Average Plaque Area (mm^2)	7.30 ± 1.85	7.84 ± 1.92	7.55 ± 1.58	6.79 ± 1.90	0.0095	0.0514	0.0001

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days

In both ABSORB Cohort B1 and B2, Absorb demonstrated good patency out to 5 years.

Optical Coherence Tomography (OCT) Analysis

Cohort B1: Serial OCT analysis at baseline, 6 months, 2 and 5 years were available in 13 lesions from Group 1 (**Table X-11**). There were no significant changes in the mean scaffold area between post procedure and 6 months. At 6-month follow-up, the neointimal located between and over the struts represents a surface area of 1.53 mm^2. As a result, the mean and minimal luminal area and flow significantly. Strut coverage was almost complete (~98%) at 6 month follow-up. From 6 months to 2 years the mean strut core area continued to decrease from 0.22 mm^2 to 0.15 mm^2 ($p = 0.0012$), indicating continued strut bioresorption. The mean scaffold area increased from post-procedure (7.55 mm^2) to 2 years (8.54 mm^2, $p = 0.0171$) indicating loss of mechanical integrity of the scaffold and potential expansion of the vessel. As a result, mean lumen area remain unchanged despite the minimal increase in mean neointimal area from 6 months to 2 years (1.53 mm^2 vs. 2.22 mm^2, $p = 0.0012$). Between 2 and 5 years, mean luminal and flow areas remain comparable. At 5-year follow-up, all struts have completely resorbed; therefore, scaffold area cannot be assessed.

Table X-11 Paired OCT Results at Post-procedure, 6 Months, 2 and 5 Years (Group 1, ITT Population)

Group 1 OCT (paired)	Post-procedure (L = 13)	6-month (L = 13)	2-year (L = 13)	5-year (L = 13)	p-value post vs. 6m*	p-value 6m vs. 2y*	p-value post vs. 2y*	p-value 2y vs. 5y*
Mean Neointimal Area (mm^2)	NA	1.53 ± 0.36	2.22 ± 0.47	NA	NA	0.0012	NA	NA
Mean Strut Core Area (mm^2)	0.22 ± 0.03	0.22 ± 0.06	0.15 ± 0.02	NA	0.8926	0.0012	0.0002	NA
% of Uncovered Struts	96.97 ± 6.83	1.80 ± 1.63	1.40 ± 2.37	NA	0.0002	0.1909	0.0002	NA

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.

Note: Data are presented as Mean ± SD or %. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

Cohort B2: Serial OCT imaging at baseline, 1, 3 and 5 years were available in 17 lesions from Group 2 (**Table X-12**). There were no significant changes in mean and minimal scaffold area between post-procedure and 1 year although the strut core area decreased significantly from 0.19 mm2 to 0.16 mm^2 (an optical sign of bioresorption). The neointimal growth was low and well controlled at 1.42 mm^2; as a result, there was a minimal reduction in the functional lumen at 1 year as demonstrated by the decrease in mean and minimal flow area as well as an increase in lumen area stenosis from immediately post procedure to 1 year. The OCT analysis revealed scaffold enlargement between 1 year and 3 years (mean scaffold area of 7.45 mm^2 at 1 year vs. 8.61 mm^2 at 3 years, $p = 0.0003$) consistent with IVUS results. Lumen area remained fairly constant, despite the minimal increase in neointimal hyperplasia at 3 years (mean neointimal area of 1.42 mm^2 at 1 year vs. 2.39 mm^2 at 3 years, $p < 0.0001$). Strut coverage was almost complete at 1 year (~97%), which was further increased to ~98% at 3 years. Mean luminal and flow areas remain stable from 3 to 5 years. At 5-year follow-up, struts were no longer identifiable in any Group 2 patients, suggesting complete bioresorption.

Table X-12 Paired OCT Results at Post-procedure, 1, 3 and 5 Years (Group 2, ITT Population)

Group 2 OCT (paired)	Post-procedure (L = 17)	1-year (L = 17)	3-year (L = 17)	5-year (L = 17)	p-value post vs. 1y*	p-value 1y vs. 3y*	p-value post vs. 3y*	p-value 3y vs. 5y*
Mean Neointimal Area (mm^2)	NA	1.42 ± 0.71	2.39 ± 0.68	NA	NA	< 0.0001	NA	NA
Mean Strut Core Area (mm^2)	0.19 ± 0.03	0.16 ± 0.02	0.20 ± 0.03	NA	0.0079	0.0002	0.4307	NA
% of Uncovered Struts	97.65 ± 5.56	3.03 ± 2.81	1.70 ± 1.59	NA	< 0.0001	0.0131	< 0.0001	NA

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days

Multi-slice Computed Tomography (MSCT) Analysis (Full cohort)

Unlike metal stents where visualization or evaluation of the in-stent lumen by MSCT is challenging owing to the blooming artefact caused by metallic stent struts, it was possible to assess quantitatively the scaffolded segment in 61 lesions in Cohort B at 18 months. MSCT allowed non-invasive assessment of segments treated with Absorb scaffold and demonstrated no significant re-stenosis with % area stenosis of 22.73 ± 22.41% and mean lumen area of 5.15 ± 1.35 mm^2 (**Table X-13**).

Table X-13 Key MSCT of ABSORB Cohort B (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

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

Note: Follow-up window was: 18 months ± 28 days

Unlike permanent metal implants, polymeric implants do not cause imaging artifacts during non-invasive CT or MR evaluation. The data from ABSORB Cohort B demonstrates that Absorb provides the additional benefit that a polymeric bioresorbable scaffold may be more compatible with the growing usage of non-invasive follow-up imaging than is the case with metallic stents. Potentially this may facilitate patient management and providing economic benefits.

Vasomotor Function Outcomes

The 5 year data demonstrated significantly improved vasomotor function at the 3 year and 5 year follow-up. At the 3 year follow-up, 27 patients from Group 2 underwent vasomotor function test with nitrate administration (**Table X-14**). The in-scaffold mean lumen diameter increased from 2.45 ± 0.37 mm (pre-nitrate) to 2.50 ± 0.39 mm (post-nitrate) ($p = 0.0050$). At the 5 year follow-up, a total of 57 patients from the full Cohort B (23 from Group 1 and 34 from Group 2) completed vasomotor function tests with nitrate administration (**Table X-14**). The in-scaffold mean lumen diameter increased from 2.48 ± 0.38 mm (pre-nitrate) to 2.56 ± 0.37 mm (post-nitrate) ($p < 0.0001$).

Table X-14 Vasomotor Function by Nitroglycerine Injection at 2, 3 and 5 years (PTE Population)

	Mean Luminal Diameter (mm)						**P-values*, Pre vs Post**		
	Group B1 2Y (L=33)		**Group B2 3Y (L=47)**		**Full Cohort 5Y (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

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables

Note: Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

D. ABSORB EXTEND

The ABSORB EXTEND trial was established to expand treatment with Absorb in a broader patient population around the world (outside of the USA), to collect clinical data with minimum follow-up imaging, and to increase lesion complexity by including subjects with longer lesions treated with either overlapping of two Absorb or use of longer length Absorb.

D1. Study Design

ABSORB EXTEND was a prospective, non-randomized single arm, open-labeled multi-center clinical trial that was planned to register approximately 1000 subjects at up to 100 global sites. Subjects registered can be treated with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels; target lesions between > 22 mm and ≤ 28 mm in length were to be treated by overlapping of two Absorb scaffolds.

The primary objective of the ABSORB EXTEND trial was to continue the assessment of the safety and performance of Absorb. A primary endpoint for hypothesis testing was not established for this trial. Descriptive statistics were used to summarize baseline and clinical

outcome data. The clinical results presented in this section are based on the intention-to-treat population.

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 18 years of age and had evidence of myocardial ischemia (stable or unstable angina, or silent ischemia). Female subjects with childbearing potential had to have a negative pregnancy test within 7 days prior to the index procedure. The subjects who were considered eligible based on the general inclusion and exclusion criteria were invited to enroll in the study and provided written informed consent. The final assessment for eligibility for subject registration was conducted based on pre-procedure angiographic/IVUS results.

Subjects with target vessel diameter of ≥ 2.0 mm and ≤ 3.3 mm by on-line quantitative coronary angiography (QCA) or IVUS, lesion length ≤ 28 mm, %DS of ≥ 50% and < 100%, TIMI flow of ≥ 1 could be registered. 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; evidence of myocardial bridging; restenotic from previous intervention; target vessel containing thrombus; other clinically significant lesions in the target vessel or side branch, evidence of myocardial bridging in the coronary anatomy. Subjects with history of paradoxical exercise-induced vasoconstriction consistent with myocardial bridging in the coronary anatomy were also excluded.

PCI for other lesions in a non-target vessel could be done ≥ 30 days prior to or if planned to be done 6 months after the index procedure. PCI for other lesions in the target vessel could be done > 6 months prior to or if planned to be done 6 months after the index procedure.

Subjects meeting all inclusion and exclusion criteria, who signed informed consent and had an investigational device delivered beyond the guide catheter were considered to be registered and were part of intent-to-treat (ITT) analysis.

Medication and Follow-Up

Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of thienopyridine antiplatelet (≥ 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. All patients were required to receive anticoagulation and other therapy during stent implantation according to the standard of care at the clinical site. All patients were to be maintained on 75 mg clopidogrel daily or 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.

Subjects are evaluated at 30 days, 180 days, 12 months, 18 months (subset), 2 years and 3 years.

Clinical Endpoints

Key clinical endpoints include: Acute success, Major Adverse Cardiac Event (MACE), Target Lesion Failure and Target Vessel Failure (TVF) and their components at each follow-up. Descriptive statistics were used to summarize baseline and clinical outcome data for each follow-up.

D2. Accountability of Subjects

The ABSORB EXTEND trial registered 812 subjects at 56 investigational sites between January 11, 2010 and October 2, 2013. A total of 874 lesions were treated, with 7.6% (62/812) of the subjects with two target lesions and 10.5% (85/812) with long lesions treated with planned overlapping Absorb scaffolds. One-year data are available for all 812 subjects.

D3. Study Population Demographics and Baseline Parameters

In the ABSORB EXTEND trial the mean age was 61.12 ± 10.75 years and 74.3% (603/812) of the subjects were male. Regarding medical risk factors, 23.2% (188/812) of the subjects were tobacco users, 69.3% (563/812) had hypertension requiring medication, and 67.7% (550/812) had dyslipidemia requiring medication. There were 36.7% (276/752) of the subjects with family history of premature CAD, and 28.5% (230/807) with prior MI history. In addition, 26.5% (215/812) of the subjects were diabetic, with 24.1% (196/812) requiring medication.

D4. Safety and Efficacy Results

The clinical results are presented in **Table X-15**, below. These analyses are based on the ITT population. The observed TLF rate at 1-year was 5.0% (41/812).

Table X-15 ABSORB EXTEND Clinical Results (ITT population) - 1-Year Results

	Absorb (N=812)
COMPOSITE EFFICACY AND SAFETY	
TLF	5.0% (41/812)
EFFICACY	
Ischemia-Driven TLR	2.3% (19/812)
TLR, CABG	0.2% (2/812)
TLR, PCI	2.1% (17/812)
Ischemia-Driven TVR	2.8% (23/812)
SAFETY	
All Death	1.1% (9/812)
Cardiac Death	0.7% (6/812)
Vascular Death	0.1% (1/812)
Non-cardiovascular death	0.2% (2/812)
TV-MI	3.3% (27/812)
QMI	1.0% (8/812)
NQMI	2.3% (19/812)
All MI	3.3% (27/812)
QMI	1.0% (8/812)
NQMI	2.3% (19/812)
Cumulative ARC-defined Definite + Probable Stent/Scaffold Thrombosis (0-365 days)	1.0% (8/809)
Acute (< 1 day)	0.0% (0/812)
Sub-Acute (1-30 days)	0.6% (5/812)
Late (31-365 days)	0.4% (3/807)

Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI per protocol definition per WHO

E. ABSORB II Randomized Controlled Trial

The ABSORB II Randomized Controlled Trial (ABSORB II) is the CE mark post-approval randomized clinical trial designed to compare the safety, efficacy and performance of Absorb compared to XIENCE in the treatment of *de novo* native coronary artery lesions.

E1. Study Design

The ABSORB II is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial (Europe and New Zealand) registering 501 subjects at 46 sites. Target lesions were up to 2 *de novo* native coronary artery lesions, each located

in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 mm and 3.8 mm as estimated by on-line quantitative coronary angiography (QCA), and a lesion length of ≤ 48 mm. Planned overlapping of study devices was allowed for treatment of long lesions.

The co-primary endpoints of the study are vasomotor function assessed by change in mean lumen diameter between pre- and post-nitrate at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both by angiography. Vasomotor function is tested for superiority using a t-test at two-sided alpha of 0.05. Minimum Lumen Diameter change is tested for non-inferiority (non-inferiority margin of 0.14mm) using an asymptotic test at one-sided alpha of 0.05. If non-inferiority is met with higher value in the Absorb arm, then superiority will be tested using a t- test at two-sided alpha of 0.05. Analyses of secondary endpoints are descriptive.

Clinical Inclusion and Exclusion Criteria

Enrollment in ABSORB II was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Patients were eligible if they were at least 18 years of age and less than 85 years of age, male or female, and had evidence of myocardial ischemia. Pregnant or nursing subjects and those who plan pregnancy in the period up to 3 years following index procedure could not be included (female subjects of child-bearing potential must have a negative pregnancy test done within 28 days prior to the index procedure). The final assessment for eligibility for subject registration was conducted based on pre-procedure angiographic results.

Key angiographic inclusion criteria included: vessel D_{max} by on-line QCA of ≥ 2.25 mm and ≤ 3.8 mm and lesion length ≤ 48 mm; % diameter stenosis (%DS) of ≥ 50% and < 100%; TIMI flow of ≥ 1. Key angiographic exclusion criteria included: aorto-ostial location; left main trunk 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; involving a bifurcation lesion with side branch ≥ 2 mm in diameter, or with a side branch < 2mm in diameter requiring guide wire protection or dilatation.

Medication and Follow-Up

Subjects must receive a 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. The loading dose may be omitted for those subjects on chronic therapy for ≥ 7 days prior to the index procedure. All subjects must be maintained on an ADP antagonist (≥ 75 mg of clopidogrel, or ≥ 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.

Clinical follow-up is planned at 30 days, 180 days and at 1, 2, 3, 4 and 5 years. All subjects undergo coronary angiography, IVUS (gray-scale and IVUS-VH) at pre- and post-device

implantation and at 3-year follow-up. A Multi Slice Computed Tomography (MSCT) scan is mandatory for all subjects in the Absorb arm at 3 years follow-up.

Clinical Endpoints

The co-primary endpoints of the study are vasomotor function assessed by change in mean lumen diameter between pre- and post-nitrate at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both by angiography. The major secondary endpoint was in-scaffold/in-stent mean lumen area change, from post-procedure to 3 years by IVUS. Typical clinical endpoints in coronary stent trials are also evaluated at each clinical follow-up time point and typical angiographic and IVUS endpoints are evaluated at post-procedure and at 3 years. MSCT endpoints include descriptive analysis of vascular and scaffold morphology and quantitative measurement of treated segment at 3 years (Absorb only). Subject's quality of life is assessed pre-procedure, and post-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).

One-year clinical outcomes are presented in this section.

E2. Accountability of Subjects

Between Nov 28th, 2011, and June 4th, 2013, 501 subjects from 46 investigational sites in Europe and New Zealand, were registered in the ABSORB II trial and randomly assigned to the Absorb arm (335 subjects) or the XIENCE arm (166 subjects). A total of 364 lesions were treated in the Absorb arm, and 182 lesions in the XIENCE arm. Early termination at 1 year, due to consent withdrawal or death, affected 1.8% (6/335) of the subjects in the Absorb arm and 1.2% (2/166) in the XIENCE arm. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

E3. Study Population Demographics and Baseline Parameters

The mean age was 61.5 ± 10.0 and 60.9 ± 10.0 years in the Absorb 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. In the study population, there was high prevalence of comorbidities of hypertension (69.0% vs. 71.7% for the Absorb and XIENCE arms, respectively) and dyslipidaemia (75.2% vs. 80.1% for the Absorb and XIENCE arms, respectively). Over 20% of the population were diabetic (23.9% vs. 24.1% for the Absorb and XIENCE arms, respectively). The proportion of patients with triple (or more) of diseased, native, major epicardial coronary arteries were 2.4% (8/335) in the Absorb arm and 3.6% (6/166) in the XIENCE arm.

E4. Safety and Efficacy Results

No patients have yet reached the primary imaging endpoint of the study set at 3-year follow-up. The 1-year safety and efficacy results are presented in **Table X-16**. These analyses are based on the intent-to-treat population. The TLF rate at 1 year was 4.8% in the Absorb arm and 3.0% in the XIENCE arm.

Table X-16 ABSORB II Clinical Results (ITT Population) - 1-Year Results

	Absorb (N=335)	XIENCE (N=166)	Difference [95% CI][1]
COMPOSITE EFFICACY AND SAFETY			
TLF	4.8% (16/331)	3.0% (5/165)	1.80% [-2.48%, 5.16%]
EFFICACY			
Ischemia-Driven TLR	1.2% (4/331)	1.8% (3/165)	-0.61% [-4.08%, 1.60%]
TLR, CABG	0.0% (0/331)	0.0% (0/165)	0.00% [NA]
TLR, PCI	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% [NA]
Vascular Death	0.0% (0/331)	0.0% (0/165)	0.00% [NA]
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%]
Cumulative ARC-defined Definite + Probable Stent/Scaffold 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% [NA]

[1] By Newcombe score method
Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition

F. ABSORB Japan Randomized Controlled Trial

The ABSORB Japan Randomized Controlled Trial (ABSORB Japan) is the randomized pivotal trial for Japan approval of Absorb that evaluate safety and effectiveness of Absorb in the treatment of subjects with ischemic heart disease caused by *de novo* native coronary artery lesions in a Japanese population in comparison to XIENCE.

F1. Study Design

The ABSORB Japan is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial in Japan registering 400 subjects. Treatment of up to 2 *de novo* native coronary artery lesions is permissible, with each lesion located in different major epicardial vessels, with D_{max} of ≥ 2.5 mm and ≤ 3.75 mm and lesion length of ≤ 24 mm, by visual estimation. Planned overlapping treatment of the target lesion is not allowed. If a subject has only one target lesion eligible to be treated with the study device, the additional non-target lesion can be treated with XIENCE. Subjects were allocated to one of three intravascular imaging subgroups, IVUS (150 subjects), OCT 1 (125 subjects), or OCT 2 (125 subjects) based on method and schedule of intravascular imaging.

The primary endpoint of the study is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year, non-inferiority against the control. The primary endpoint is evaluated using the difference in event rates in the ITT population. The hypothesis test is designed to show non-inferiority of Absorb to XIENCE (non-inferiority margin of 8.6%) using the likelihood score method by Farrington and Manning at a one-sided alpha of 0.025.

Clinical Inclusion/Exclusion Criteria

Subjects were eligible if they were at least 20 years of age, male or female, and had evidence of myocardial ischemia. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following the index procedure could not be included (female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure). Prior PCI to the target vessel ≤ 12 months or to the non-target vessel ≤ 24 hours (if successful and uncomplicated) or ≤ 30 days (otherwise), planned PCI either in target or non-target vessels after the index procedure were not allowed. The final assessment of subject eligibility was done based on pre-procedure (baseline) angiography and pre-dilatation results. Subjects had to sign an informed consent form in order to enroll in the study.

Key angiographic inclusion criteria included: D_{max} of ≥ 2.5 mm and ≤ 3.75 mm and lesion length ≤ 24 mm; % diameter stenosis (%DS) of ≥ 50% and < 100%; TIMI flow of ≥ 1 by visual estimation. Key angiographic exclusion criteria included: aorto-ostial location; left main trunk 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; involving a bifurcation lesion with side branch ≥ 2 mm in diameter, requiring

protection guide wire, or requiring dilatation. Successful pre-dilatation with < 40% residual DS and TIMI-3 flow, and without angiographic complications, dissections, chest pain and ST changes > 5 minutes is required.

Medication and Follow-Up

Subjects must receive a 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. 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 index procedure.

Clinical follow-up is planned 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. The IVUS subgroup would undergo IVUS follow-up at post-procedure and 3 years. The OCT 1 subgroup would undergo OCT follow-up at post-procedure, 2 and 3 years. The OCT 2 subgroup would undergo OCT follow-up only at 3 years (no post-procedure OCT). As additional sub-studies in selected sites, MSCT scan at 13 months and 3 years (150 subjects), and ACh-induced vaso-reactivity test at 4 years would occur (120 subjects).

Clinical Endpoints

The primary endpoint of the study is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year. Powered secondary endpoints are the in-segment late loss (LL) at 13 months by angiography (non-inferiority), the in-device mean lumen area change, from post-procedure to 3 years by IVUS (superiority) and the in-device mean lumen diameter change, between pre- and post-nitrate infusion at 3 years by angiography (superiority). The powered secondary endpoint of in-segment LL is tested for non-inferiority (non-inferiority margin of 0.195 mm) using an asymptotic test at one-sided alpha of 0.05. For powered imaging secondary endpoints of vasomotor function and change of mean lumen area, the pooled subjects from the Imaging Cohort of ABSORB III and ABSORB Japan are used and superiority tests are performed using a t-test at two-sided alpha of 0.025.

Typical clinical endpoints in coronary stent trials are also evaluated at each clinical follow-up time point.

F2. Accountability of Subjects

Between April 27th, 2013 and December 27th, 2013, 400 subjects from 38 investigational sites in Japan were registered in the ABSORB Japan, and randomly assigned to the Absorb arm (266 subjects) or the XIENCE arm (134 subjects). A total of 275 lesions were treated in the Absorb arm, and 137 lesions in the XIENCE arm. Early termination at 1 year, due to consent withdrawal or death, affected 4 subjects in the Absorb arm and 1 subject in the XIENCE arm. Two subjects (1 in the Absorb arm and 1 in the XIENCE arm) who withdrew

consent but had no known DMR (Death, MI, Revascularization) event were excluded from the analysis. All subjects have completed their 1-year follow-up and clinical follow-up through 5 years is ongoing.

F3. Study Population Demographics and Baseline Parameters

The mean age was 67.1 ± 9.4 years in the Absorb arm and 67.3 ± 9.6 years in the XIENCE arm. The population of the ABSORB Japan was predominantly male (78.9% in the Absorb arm, 73.9% in the XIENCE arm). In the study population, there was a high prevalence of comorbidities of hypertension (78.2% vs 79.9% for the Absorb and XIENCE arms, respectively) and dyslipidemia (82.0% vs 82.1% for the Absorb and XIENCE arms, respectively). Over 30% of the population was diabetic (36.1% vs 35.8% for the Absorb and XIENCE arms, respectively). The proportion of patients with two (or more) lesions treated were 10.9% (29/266) in the Absorb arm and 9.7% (13/134) in the XIENCE arm.

F4. Safety and Efficacy Results

The safety and efficacy results for the ABSORB Japan are presented in **Table X-17**. The Absorb arm was non-inferior to XIENCE with a non-inferiority p-value of < 0.0001 for observed TLF rates at 1 year. The observed TLF rate at one year was 3.8% (5/133) in the XIENCE arm and 4.2% (11/265) in the Absorb arm (per protocol MI definition).

Table X-17 ABSORB Japan Clinical Results (ITT Population) - 1-Year Results

	Absorb (N=266)	XIENCE (N=134)	Difference [95% CI][1]
COMPOSITE EFFICACY AND SAFETY			
TLF	4.2% (11/265)	3.8% (5/133)	0.39% [-4.68%, 4.18%]
EFFICACY			
Ischemia-Driven TLR	2.6% (7/265)	2.3% (3/133)	0.39% [-4.00%, 3.48%]
TLR, CABG	0.0% (0/265)	0.0% (0/133)	0.00% [-2.81%, 1.43%]
TLR, PCI	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%]
Cumulative ARC-defined Definite + Probable Stent/Scaffold 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] By Newcombe score method
Note: 1-year timeframe includes a window of ± 28 days
Note: N is the total number of subjects
Note: MI is per protocol definition

G. Pharmacokinetics - ABSORB III PK

G1. Study Design

ABSORB III PK is a sub-study of ABSORB III with the objective of determining the pharmacokinetics of everolimus delivered by the Absorb scaffold in a separate and non-randomized cohort of subjects who only received Absorb, with a maximum of two *de novo*

native coronary artery lesions after implantation of the Absorb scaffold. ABSORB III PK is a prospective, open-label, non-blinded study that enrolled 12 subjects at 2 clinical sites.

In order to enroll in the PK sub-study, subjects had to sign an informed consent form and meet the general and angiographic inclusion criteria, and could not have any general or angiographic exclusion criteria, as set forth in the ABSORB III clinical trial protocol. One exception was that, as opposed to the ABSORB III primary analysis group, the ABSORB III PK sub-study did not allow treatment of non-target lesions.

Arterial or venous blood was scheduled to be drawn at baseline (prior to placement of the first Absorb), at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 168, 336 and 720 hours (30 days) post-Absorb implantation. In addition to having their blood drawn, all PK subjects will be clinically followed through 5 years, with visits at 30 and 180 days, and at 1, 2, 3, 4 and 5 years.

Whole blood samples were temporarily stored at -70°C at the investigational site and were shipped to a central core laboratory. The concentration of everolimus in whole blood samples was determined by a validated Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC-MS/MS) assay in the bioanalytical core laboratory. The lower limit of quantification (LLOQ) of everolimus in the blood samples was 0.1 ng/mL. Pharmacokinetic analysis of the everolimus blood concentration-time data was conducted by the pharmacokinetics core laboratory using non-compartmental methods. The following parameters were calculated: C_{max}, t_{max}, AUC_{24h}, AUC_{last}, $AUC_{0-\infty}$, λ_z, $t_{1/2}$, CL.

C_{max} (ng/mL)	Maximal observed blood everolimus concentration
t_{max} (h)	Time to reach the maximal observed blood everolimus concentration
AUC_{24h} (ng*h/mL)	Area under the blood everolimus concentration vs. time curve from time 0 up to 24 hours post placement of the last Absorb, calculated by the linear up/log down trapezoidal method
AUC_{last} (ng*h/mL)	Area under the blood everolimus concentration vs. time curve from time 0 up to the last quantifiable concentration, calculated by the linear up/log down trapezoidal method
$AUC_{0-\infty}$ (ng*h/mL)	Area under the blood everolimus concentration vs. time curve from time zero and extrapolated to infinite time, calculated as: $AUC_{0-\infty} = AUC_{last} + (C_{last}/\lambda_z)$ The percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{0-\infty ex}$) is calculated as: $\%AUC_{0-\infty ex} = 100*(AUC_{0-\infty} - AUC_{last})/ AUC_{0-\infty}$
λ_z (1/h)	Terminal rate constant, determined by linear regression of terminal points of the ln-linear analyte concentration-time curve
$t_{1/2}$ (h)	Terminal half-life, calculated as $t_{1/2} = 0.693/\lambda_z$
CL (L/h)	Clearance, calculated as Dose/$AUC_{0-\infty}$

Whole blood concentration-time data were listed by nominal sampling time. If an actual sampling time deviated by 20% or more from the scheduled time, this sample was excluded from descriptive statistics in the blood concentration-time table. Summary statistics include sample size (N), mean, standard deviation (SD), percentage of coefficient of variation (%CV), geometric mean, median, minimum, and maximum. To explore dose proportionality of everolimus, a regression analysis on dose-normalized (to 1 µg) PK parameters (C_{max}, AUC_{24h}, AUC_{last}, and $AUC_{0-\infty}$) for everolimus was performed using the regression procedure (PROC REG) in SAS.

G2. Accountability of Subjects

A total of 12 subjects were registered in the PK sub-study from two investigational sites in the US. The first subject was registered on June 2, 2014 and the last subject was registered on September 17, 2014. There was no early subject termination from the study at or before the 30-day follow-up visit.

G3. Study Population Demographics and Baseline Parameters

The characteristics of the PK sub-study participants are similar to the characteristics of the ABSORB III primary analysis group. The PK patient population consisted of predominantly males (91.7%). The mean age was 60.1± 10.5 years. In the PK sub-study population, there was a high prevalence of comorbidities of hypertension (100%) and dyslipidemia (100%), both requiring medication. Over 30% (33.3%) of the population were diabetic. All patients had a single *de novo* target lesion in a native coronary artery.

G4. Results

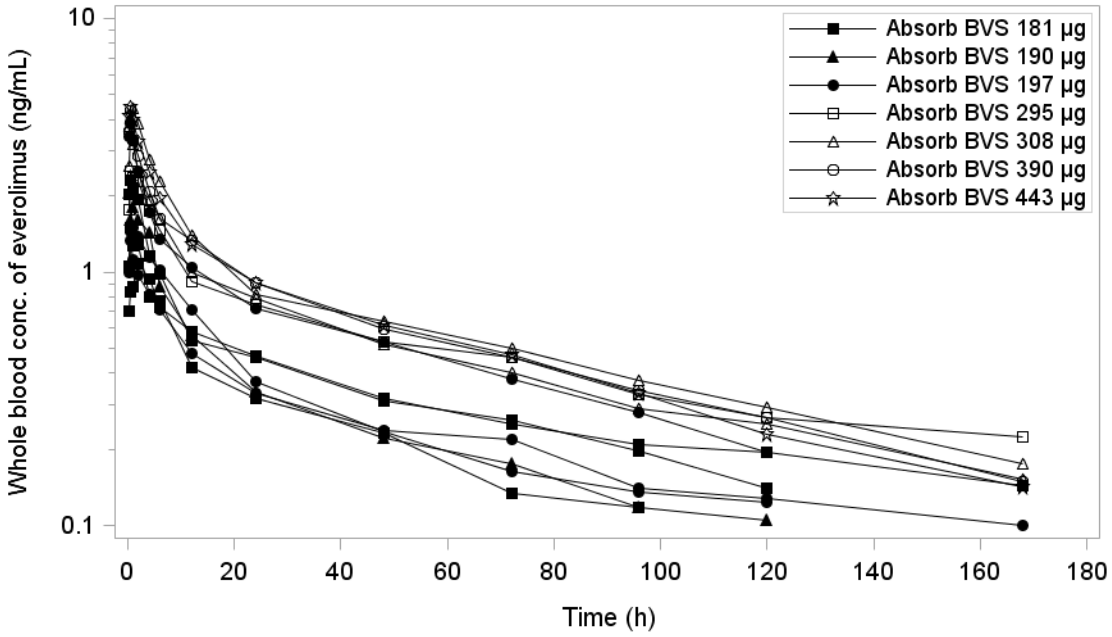
The pharmacokinetics (PK) of everolimus eluted from the Absorb scaffold were evaluated in 12 subjects. Four subjects received 2 Absorb and 8 subjects received one Absorb, with the diameters of 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18, and 28 mm. The total everolimus dose ranged from 181 to 443 µg.

The results of the ABSORB III PK sub-study are presented in **Figure X-1** (everolimus blood concentration-time curve) and **Table X-18** (everolimus PK parameters) below. Everolimus 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. Everolimus concentrations were low but measurable up to 168 hours (7 days) after last scaffold deployment.

The maximum observed everolimus concentration (C_{max}) values increased with dose and ranged from 1.085 to 4.460 ng/mL across the dosage range studied. Similarly, individual AUC_{24h} (ranging from 12.09 to 44.22 ng*h/mL), AUC_{last} (ranging from 25.37 to 104.6 ng*h/mL) and $AUC_{0-\infty}$ (ranging from 33.15 to 120.8 ng*h/mL) increased proportionally with

dose. Further, dose-normalized C_{max} and area under the concentration- time curve (AUC^4) were comparable across the total scaffold dose, indicating that the systemic exposure increased proportionally with the total scaffold dose. Overall, intersubject variability was acceptable[5]: 23.3% and 35.6% for dose-normalized $AUC_{0-\infty}$ and C_{max}, respectively.

The results of this study are consistent with previous clinical studies using the XIENCE V stent and in accordance with the preclinical profile of everolimus. Individual C_{max} values (1.085 to 4.460 ng/mL) were slightly higher than the minimum systemic therapeutic level of 3.0 ng/mL necessary to be maintained for effective prevention of organ rejection[6,7]. However, as opposed to a chronic systemic therapy, everolimus blood concentrations decline rapidly after Absorb implantation. By 4 hours after the last scaffold deployment, blood concentrations were below 3.0 ng/mL (chronically maintained therapeutic level necessary for effective organ rejection prevention) in all subjects. The rapid disappearance of everolimus from the circulation after implantation of Absorb, limits the extent of systemic exposure, and is therefore safe.



Note: 181 µg (n=3 subjects); 190 µg (n=1 subject); 197 µg (n=3 subjects); 295 µg (n=1 subject); 308 µg (n=2 subjects); 390 µg (n=1 subject); 443 µg (n=1 subject).

Figure X-1 ABSORB III PK - Combined Whole Blood Concentration-Time Curves of Everolimus

[4] AUC_{24h}:from time 0 to 24 hours; AUC_{last}: from time 0 up to the last quantifiable concentration; $AUC_{0-\infty}$: from time zero and extrapolated to infinite time

[5] Intersubject variability was considered acceptable based on an intersubject variability > 30% is considered very high.

[6] Kovarik, J.M., et al., Everolimus in de novo cardiac transplantation: pharmacokinetics, therapeutic range, and influence on cyclosporine exposure. J Heart Lung Transplant, 2003. 22(10): p. 1117-25.

[7] Starling, R.C., et al., Therapeutic drug monitoring for everolimus in heart transplant recipients based on exposure-effect modeling. Am J Transplant, 2004. 4(12): p. 2126-31

Table X-18 ABSORB III PK - Whole Blood Pharmacokinetic Parameters in Subjects Following Absorb Implantation

Dose Range (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2term}$ (h)	AUC_{24h} h*ng/mL	AUC_{last} h*ng/mL	$AUC_{0-\infty}$ h*ng/mL	CL (L/h)
	Median (range)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
181 - 443	0.55 (0.17-2.37)	2.74 ± 1.308	67.20 ± 18.8	24.84 ± 11.04	61.88 ± 28.41	76.05 ± 30.21	3.551 ± 0.8791

H. Conclusion of Clinical Studies

Principal safety and effectiveness information for the Absorb GT1 BVS System is derived from ABSORB III and is supported by data from ABSORB Cohort B, ABSORB EXTEND, ABSORB II, and ABSORB Japan. In addition, the safety of everolimus, the drug eluted from the Absorb scaffold, was evaluated in the ABSORB III PK sub-study.

Results from ABSORB III, conducted in the US and Australia, demonstrated that Absorb was non-inferior to XIENCE for the primary endpoint of TLF (a composite of: cardiac death, target-vessel myocardial infarction and ischemia-driven target lesion revascularization) at 1-year. Similarly, in the ABSORB Japan, Absorb was also found to be non-inferior to XIENCE for the primary endpoint of TLF at 1 year, in a Japanese population. Finally, in the ABSORB II (post-approval trial for CE mark, conducted in Europe and New-Zealand), there was no statistically significant difference in TLF rate at 1 year between the Absorb arm and the XIENCE arm.

In addition, IVUS imaging results from ABSORB Cohort B demonstrated late lumen enlargement, and increase in scaffold area, at 2 and 3 years. Complete resorption of the scaffold was observed at the 5-year follow-up, along with return of vasomotor function.

The pharmacokinetic profile of everolimus was adequately characterized in the ABSORB III PK sub-study. Results showed a rapid disappearance of everolimus from the circulation after implantation of the Absorb scaffold, which limits the extent of systemic exposure. The pharmacokinetic profiles seen with the Absorb are thus considered to be safe.

Taken together, the results from the ABSORB family of clinical trials demonstrate that Absorb is safe and effective for the treatment of ischemic heart disease caused by up to two *de novo* native coronary artery lesions.

XI. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

{FDA to insert Conclusions Drawn from the Preclinical and Clinical Studies}

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

{FDA to insert Panel Recommendations}

XIII. CDRH DECISION

{FDA to insert CDRH Decision}

XIV. APPROVAL SPECIFICATIONS

{FDA to insert Approval Specifications}